Modelling and synthesis of pharmaceutical processes: moving from batch to continuous

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Doctor of Philosophy Thesis

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Kgs. Lyngby, Denmark

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PREFACE

This thesis is submitted as partial fulfilment of the requirements for the Doctor of Philosophy (PhD) degree at the Technical University of Denmark (DTU). The PhD project was carried out at the research group "*PSE* for *SPEED*" at the Department of Chemical and Biochemical Engineering from October 2013 to September 2016 under the guidance of Professor Rafiqul Gani as the main supervisor and Professor John M. Woodley as co-supervisor. The project has been financed by the Technical University of Denmark (DTU).

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I couldn't do much without endless support from my whole family, especially my parents (Ioannis and Chrisi) and my brother (Giorgos). They have always believed in me and supported me. I will be forever grateful for everything they did for me.

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Emmanouil (Manolis) Papadakis

September 2016, Kgs. Lyngby

ABSTRACT

Research in pharmaceutical process development has gained a lot of interest over the last years. Long development times, increasing R&D costs, increasing competition, and short patent duration are some of the driving forces for the increased research efforts in the field. Increased process understanding of the pharmaceutical process has resulted in major improvements in the field. Process systems engineering (PSE) approaches, which have been successfully applied in the design, analysis and optimization of chemical and petrochemical processes, might be also important for the improvement of pharmaceutical processes by providing systematic and structured solutions for the stages of the pharmaceutical process development.

In this PhD thesis, the objective is to systematize the pharmaceutical process development in order to enhance process understanding by creating a data-rich environment and to investigate/evaluate opportunities for continuous operation. To achieve the mentioned objectives the use of an integrated framework based on systematic model-based methods and tools is proposed. Computer-aided methods and tools are used to generate process knowledge and to evaluate different operational scenarios.

The developed framework is divided into four main sections: the reaction pathway, reaction analysis, separation synthesis and process evaluation-operation based on evaluation. In the first section, the selection of the reaction pathway to produce a desired active ingredient is examined. A reaction database for small pharmaceutical molecules, including information for reactions, the solvent role and processing information, has been developed to assist the reaction pathway selection. In the second section, the reaction analysis, the identified individual reactions during the reaction pathway selection are analysed. The objective of the reaction analysis section is to collect reaction data and by using model-based methods to investigate possibilities of reaction improvement by evaluating the reaction conditions, the operating mode, the solvent role, and the reactor design. In the third section, alternatives for the separation of the reaction mixture are generated based on the driving force principles and evaluated based on performance criteria, such as mass and energy utilization. Finally, the overall process is simulated and evaluated in terms of productivity and environmental impact. Process optimization studies are performed by defining optimization target based on the process analysis.

The application of the developed integrated framework is highlighted through four case studies. In the first case study, the overall use of the framework is highlighted using the synthesis of ibuprofen as a motivating example. The second case study focuses on the application of the developed solvent selection methodology for solvent swap problems. The third case study focused on multiphase reaction systems and improvements through the combination of reaction-separation. Finally, model-based analysis-design is performed for the operation improvement of a glucose isomerization plant.

RESUME PÅ DANSK

Forskning i farmaceutisk procesudvikling har opnået meget interesse i de seneste år. Lange udviklingstider, øgende F&U-omkostninger, øget konkurrence og korte patentvarigheder er nogle af de drivende kræfter for den øget forskningsindsats på området. Øget procesforståelse af den farmaceutiske proces har resulteret i de store forbedringer på området. Proces systemteknik (*engelsk:* PSE) fremgangsmåder, som er blevet anvendt med succes i design, analyse og optimering af kemiske og petrokemiske processer, kan også være vigtig for forbedringen af de farmaceutiske processer ved at give systematiske og strukturerede løsninger til faserne af den farmaceutiske procesudvikling.

De centrale mål i denne afhandling er at systematisere den farmaceutiske procesudvikling for at forbedre forståelsen af processerne ved at skabe et data-rigt miljø og at undersøge / vurdere mulighederne for kontinuerlig drift. For at nå de nævnte mål foreslås en integreret systematisk platform baseret på systematiske modelbaserede metoder og værktøjer. Computerbaserede metoder og værktøjer bruges til at generere procesviden og/eller at anvende allerede tilgængelige viden til generering af data. Når detaljerede oplysninger for processen er til rådighed, kan ændringer forstås og knyttes til procesparametre og endelig forbundet med produktkvalitet og / eller andre procesydelseskriterier relateret til at omkostninger, bæredygtighed og energi.

Platformen er opdelt i fire hovedafsnit, reaktionsstien, reaktionsanalyse, separationssyntese og processimulering / -evaluering og drift. I det første afsnit, er forbedringer relateret til valget af reaktionsveje. En database af reaktioner for små farmaceutiske molekyler, herunder oplysninger om reaktionerne, solventrolle og behandling af oplysninger, er blevet udviklet for at lette valget reaktionsvej. I det andet afsnit er procesforbedringerne relateret til de enkelte reaktioner, som kan forbedres ved at evaluere reaktionsbetingelserne, driftsform, og opløsningsmidlets rolle. I tredje afsnit, er alternativer til separationen af reaktionsblandingen genereret baseret på den drivkraft principper og evalueres baseret på ydeevne kriterier såsom masse og energiudnyttelse. Endelig bliver den samlede proces simuleret og evalueret med hensyn til produktivitet og miljøpåvirkning. Procesoptimeringsstudier kan blive udført ved at definere optimeringsmålene, som er baseret på procesanalysen.

Anvendelsen af den udviklede integreret platform er fremhævet i fire forskellige casestudier. I det første casestudie, er den samlede brug af platformen fremhævet ved syntese ibuprofen som eksempel. Det andet casestudie fokusere på anvendelsen af den udviklede metode til valg af opløsningsmidler i et problem om ombytning af opløsningsmidler. Det tredje case studie fokuserer på flerfase reaktionssystemer og forbedringer gennem en kombination af reaktion-separation. Endelig blev en modelbaseret analyse-design metode brugt til driftsforbedringer af en reaktor.

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1 INTRODUCTION

1.1 Background and Motivation

Research in the field of pharmaceutical process development for the production of active pharmaceutical ingredients (APIs) and drug products has gained a lot of interest over the last years, leading to significant advances in science, technology, and engineering. Long development times, increasing R&D costs, increasing competition, and short patent duration are some of the driving forces for the increased research efforts in the field. The scientific community has demonstrated that lower production times, reduced environmental impact and increased process safety, while maintaining or increasing the required product quality, can be achieved through detailed understanding of the phenomena taking place in the system [1],[2]. Implementation of advanced process analytical technologies (PAT) through better process understanding has led to improved optimization of pharmaceutical processes [2],[3]. Introduction of new processing technologies, the "design space" concept as well as the adoption of quality-by-design (QbD) principles have also contributed to pharmaceutical process improvements [1],[2],[4].

The development of pharmaceutical processes starts with the identification of the synthesis route that leads to the production of the desired active ingredient. Improvements in the selection of the chemical/biochemical pathway might lead to improvements related to the total number of reactive steps, the overall reaction yield, reaction selectivity, operation time, waste generation, product quality, scalability, separation process, process safety, and economics [5]. The improvement in reaction pathway is usually related to the application of different chemistry that enables the synthesis of the main product through more efficient synthesis routes. Changes in reaction chemistry related to the reagents such as the reducing agent and the solvent, might be beneficial for the reaction performance [6], [7]. Other changes related to the catalysts (e.g. biocatalysis and biotechnology) can improve the conversion and increase the selectivity towards the desired product [5], [6], [7]. Finally, the implementation of new technologies, such as flow chemistry and new heating techniques can improve the overall reaction performance in terms of operation time, energy required, waste generated and productivity [8]. Given an improved chemistry, the reaction process can be further improved through optimization of the operating conditions, such as temperature, pressure, stoichiometry, and flowrate [9], [10], [11].

Additionaly, different reactor configurations or reactor types (e.g. continuous microflow) can offer significant advantages in the improvement of the reaction processes in terms of productivity, process safety, and cost [12].

Usually, processes for APIs manufacturing involve many reaction steps [7]. Separation is often required between the reaction steps to separate the reaction product from the impurities and other reaction compounds (e.g. catalyst, promoters). Selection of the separation tasks and sequence of separation task might also offer significant improvements in terms of number of unit operations [13], operation time, product quality, sustainability, and energy and solvent requirements [14].

Batch processing is often applied in pharmaceutical processes due to the slow reaction and purification steps using crystallization [2], [15]. In addition batch processes are flexible and multipurpose in multiproduct production facilities [1]. However, moving from a batch-wise production to continuous pharmaceutical manufacturing can lead to significant process improvements as the production can be obtained at lower operational costs, lower energy requirements, reduced waste and emissions and in general, lower environmental footprint. The performance of some reactive systems might benefit from the implementation of continuous processing as heat and mass transfer limitations, which are crucial for the reaction, might be improved [3, 9]. The potential risks of large volumes of hazardous materials (e.g. volatile reactants or solvents) can be avoided using continuous equipment as the reactor head space is eliminated [12] and the amount of hazardous materials present in reaction remains low. Another important aspect of the implementation of continuous manufacturing is the obtained product quality, which does not depend on process dynamics and the differences in product quality between batches is minimized [16]. Process variables (e.g. Temperature, pressure) that are directly connected to important process parameters and affect the product quality, can be precisely controlled leading thereby to a consistent steady state operation compared to uncertainties in batch operations. Regardless of the numerous advantages of continuous processing over batch manufacturing, there are some operational challenges related to clogging and equipment failure during startups and shutdowns that need to be addressed prior to the implementation of continuous manufacturing [7].

The multistep processes employed to produce pharmaceutical ingredients consists of a collection of operational tasks including reactions, separations and purification and most of these tasks require the use of solvent or a mixture of solvents to enhance process performance [17]. Despite the fact that the use of solvents improve the process performance in terms of yield and time, they have the largest contribution to the total used mass per kg of product per processing step (process mass intensity metric, PMI), which is translated to large amounts of generated waste and high energy requirement for solvent handling [7], [14]. Therefore, during the solvent selection needs to consider minimization of solvent minimization, opportunities for solvent recycle and improvement of the system needs to be taken into consideration, while for the selected solvent, the system performance in terms of yield and operation time [12, 13]. In this way, the overall sustainability of the process operation can be improved as the solvent use would be minimized, resulting in less energy intensive operations and less waste generation [7], [20], [21]. Solvent selection, is therefore, an important part of the pharmaceutical process development and different processing concerns for the involved process unit need to be taken into account, as the solvent use directly affects the overall process performance in terms of economics, sustainability and yield.

Process intensification systems that combine reaction and separation steps might have significant benefits in the development of pharmaceutical processes in terms of solvent use and product loss and ability to operate in the continuous mode [7]. In addition, hybrid operations, which facilitate in-*situ* product (or by-product) removal to shift the reaction equilibrium towards the product site, can also be beneficial for the reactive system as the selectivity towards the desired product is increased [22], [23]. Both intensified and hybrid operations have been considered in literature, however, the implementation of such new technologies might be difficult in a pharmaceutical process because of the high investment risk and the possibility of short product lifetime. Nevertheless, investigation to identify possibilities of implementing process intensification/hybrid operations and to evaluate different intensified/hybrid operations are required to demonstrate their benefit in pharmaceutical product manufacturing.

The evaluation of pharmaceutical processes in terms of sustainability, energy consumption and economics gives useful insights and a better understanding of the operation issues of pharmaceutical processes [14]. This evaluation enables the comparison of different reaction pathways [24], different unit operations for the same separation task and technologies [25], employing different chemistries, processing steps and reagents [6].

Process systems engineering (PSE) approaches, which have been widely used in other industries for process development, can assist in the development, analysis, design, evaluation, and optimization of pharmaceutical processes [26]. The adoption of PSE approaches can be very useful in assisting with the complex problem of pharmaceutical process development by decomposing the problem into smaller sub-problems that are easier to solve. The obtained knowledge from the solution of the individual problems is usually used to supplement experimental data in order to improve the decision-making process or to shift the direction of experimental studies in order to reduce their overall time and cost required [26],[27].

1.2 Objectives

The objectives of this PhD thesis are to:

- Develop an integrated systematic framework that creates a data-rich environment to enhance the process understanding and to investigate opportunities for implementation of continuous manufacturing in the pharmaceutical processes. The objective of the developed framework is to improve the development of primary pharmaceutical processes for the production of small pharmaceutical molecules in terms of overall process performance, product quality and sustainability using systematic model-based methods.
- Analyse each step of pharmaceutical process development starting from the selection of the synthesis path, to the analysis of each individual reaction, the development of the separation process and overall process evaluation/optimization.
- Develop systematic methods and tools to support the framework for process knowledge generation.
- Highlight the applicability of the developed framework through different case studies representing different problems that are found in pharmaceutical processes such as reaction pathway selection, reaction analysis, and solvent selection, batch to continuous, separation process development, process intensification, process evaluation, and operation.

1.3 Thesis Structure

The thesis has been divided into 6 main chapters:

Chapter 1. Introduction

Provides the main motivation, the background and the main objectives of this project.

Chapter 2. State-of-the-art pharmaceutical process development

Provides a review of the state-of-art for pharmaceutical process development. The chapter 2 is divided in three main sections: process modelling in pharmaceutical process, process synthesis of pharmaceutical process and batch to continuous processing. At the end of the chapter 2 conclusions are made to identify the research gaps in the field of pharmaceutical process development.

Chapter 3. Framework for pharmaceutical process development: methodology

Proposes a systematic integrated framework with the objective to assist the pharmaceutical process development by enhancing the process understanding at early stage of API development. The framework is a step-by-step procedure that assists to solve different synthesis/design problems by using systematic model-based methods.

Chapter 4. Framework for pharmaceutical process development: supporting methods and tools

Describes the methods and tools that are necessary for each step of the framework. Methods and tools that have been developed in this work are discussed in detail while other methods and tools that have been developed by other researchers are briefly described.

Chapter 5. Case studies

Describes the applications of the framework to four case studies. The first case study is focused on the application and verification of the developed framework through the conceptual example of the ibuprofen synthesis. In the second case study, a solvent selection problem is considered, solvent swap selection in pharmaceutical processes, where the application of the developed solvent swap methods has been highlighted through different examples. The third case study deals with reaction analysis and reaction-separation intensification of an enzymatic process and finally, the last case study deals with process improvement of a biochemical process using model-based methods.

Chapter 6. Conclusion and future perspectives

Describes the main conclusions and achievements of this project and give the future perspectives of this work.

2 STATE-OF-THE-ART: PHARMACEUTICAL PROCESS DEVELOPMENT

The main research advances in the field of pharmaceutical process development are related to: development of new reaction paths (which enable continuous flow synthesis), development of new technologies (to support the implementation of the continuous manufacturing), implementation of model-based approaches for analysis and system evaluation, the adoption of quality-by-design (QbD) paradigm for pharmaceutical development and the advances in process analytical technology (PAT) for design, analysis, and control. This chapter focuses on reviewing the state-of-art of pharmaceutical process development and covers key subject areas such as process modelling, process synthesis and batch to continuous manufacturing. At the end of the chapter, conclusions for the key research areas are made.

2.1 Review on process development-pharmaceutical processes

The chemical production, including agrochemical, biochemical, fine chemical and pharmaceuticals products is based on multistage-multipurpose batch/continuous production systems that involve multiple processing steps [25]. During early stages of the process development, processes have to be analysed and understood in order perform improvements in terms of productivity, time, cost, energy, safety, product quality, and sustainability.

In this project, the focus is shifted towards the process development of active pharmaceutical ingredients (APIs and NCEs (new chemical entities) small molecules MW<1000) during early stage of drug/process development which are produced via chemical or biochemical synthesis. In Figure 2.1, a simple process diagram for a pharmaceutical manufacturing process is illustrated. The process has two main parts: the primary production, where the API is synthesized and isolated in high purity and the second part, the secondary production, where the API is mixed with the excipient to formulate the final drug product (e.g. tablets or liquid). During the primary production, operations such as reactions, separations, and product purification steps are taking place. The reaction pathway (chemical and/or biological) from commercially available reagents to an API might require multiple reaction steps, from which, all or some of them might require separation (such as distillation, liquid-liquid extraction,

filtration, or membrane separation), and purification steps (such as crystallization and drying) [7]. Each production step during primary production might require different compounds such as organic solvents and catalysts [6]. The secondary pharmaceutical production consists of unit operations such as blending, granulation, and drying and drug formulation of the final product [28].

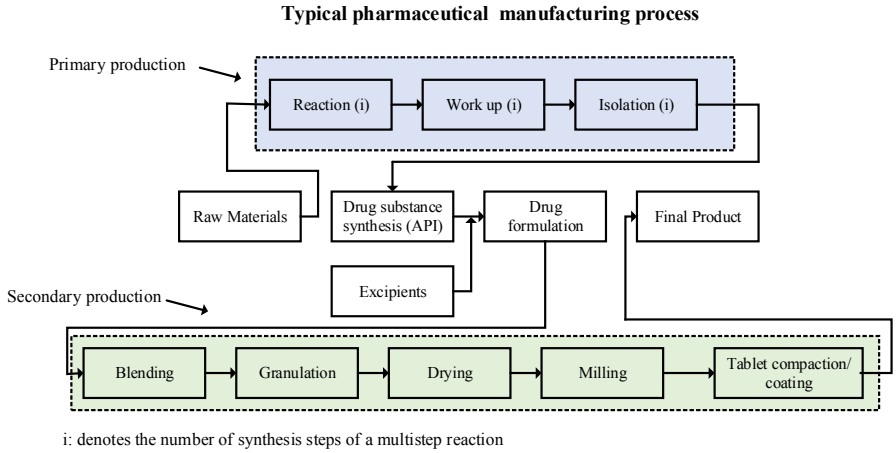


Figure 2.1. A typical process diagram for the manufacturing of pharmaceutical products. Process representation was inspired by Cervera et al. [26].

In this chapter, the state-of-art for key aspects of pharmaceutical process development such as process modelling, process synthesis, and batch to continuous manufacturing are described in detail. Then, common process synthesis/design problems of interest for pharmaceutical process are further identified and discussed. Finally, the implementation of a systematic model-based systematic approach as a solution approach is presented.

2.2 Process modelling in pharmaceutical processes

Mathematical models of different types and forms have an important role in process/product development, process design and operation, evaluation, and analysis. Models can improve the process understanding, supplement the available knowledge with new data and reduce the time of expensive experiments and the cost for development of a new products [27] [29]. Gernaey and Gani [27] presented a model-based systematic approach where the need of integrated model-based methods are needed in pharmaceutical process/product development is highlighted. This approach requires the use of tools such as databases (database of model parameters and database of chemicals), model library with predictive and process models, modelling tools to solve mathematical models and simulation tools for product and process design. Mathematical models, which are dynamic, can be efficiently used to capture the process behaviour in different operational strategies and to assist the implementation of the control strategy with the minimum requirements of resources. Process modelling has been applied to a

large number of examples related to pharmaceutical production [30]. These modelling efforts have been reviewed with respect to different unit operations involved in pharmaceutical processes.

2.2.1 Primary production

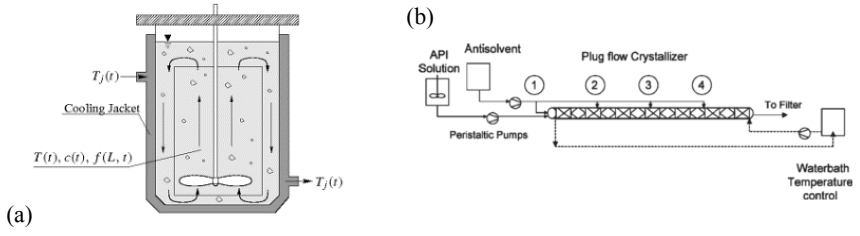
2.2.1.1 Reaction operations

The chemical synthesis of pharmaceutical active ingredients is a complex process, which depends on the operation reaction conditions such as pressure and temperature that have been selected in a way such that the reaction performance is optimized. The optimization and the design of the reaction process requires detailed understanding of the phenomena, which govern the process. To enhance the reaction process understanding and to improve systematically the reactions, mathematical models that can capture the important phenomena in the reactive system can be used. For modelling the reaction, a model for the reaction mechanism as well as a model for the reaction kinetics needs to be developed. In the literature, many kinetic studies have been published for different reaction mechanisms and processes. Recently, Grom et al. [31] developed a kinetic model for the production of Lorcaserin from 1-(2-bromoethyl)-4-chlorobenzene and allylamine via a two-step benzapine heterocyclic synthesis. The study considers other reactions that take place in parallel with the main reaction and are the sources of by-products and impurities. Based on the kinetic model, process optimization was performed with the objective to improve the reaction and the separation/purification performance [31]. The kinetics of hydrogenation of 4-isobutylacetophenone to produce p-isobutyl phenyl ethanol (an intermediate of ibuprofen synthesis) has been widely studied to optimize the reaction variables to improve the selectivity of the reaction towards the desired product by several author considering different type of catalysts, Ru/Al_2O_3 [32], Pd/SiO_2 [33], [34], and 10%Ni/Y (Y: zeolite catalyst) [35]. Many more studies involving the development and the use of kinetic models to improve the reaction performance have been reported in the literature: models for carbonylation of p-isobutyl phenyl ethanol to ibuprofen [36]-[37]; for multiphase reactions [38]-[39] , biocatalytic processes [40]–[43]. The comparison of continuous and batch reactors employing model-based methods has been studied. Tadepalli et al. [44], has compared the performance of a catalytic reactor for the hydrogenation of o-nitroanisole in microreactor and semi-batch reactor. The purpose of the study was to investigate the kinetics of the two systems and to determine the mass transfer coefficients. Based on the analysis, a guide to determine the type of reactor for the kinetic study has been proposed [44], [45].

2.2.1.2 Crystallization operation

Crystallization is a very common operation in pharmaceutical processes during the primary production as it is designed to obtain crystals of high purity, with controlled shape, size, and polymorphic form. Model-based methods have been developed and validated by several researchers considering different operational scenarios and applications with the objective to optimize the variables related to product quality. Samad et al. [46] developed a general systematic model-based framework for study of batch cooling crystallization processes. The developed framework allows the study of different chemical systems and different crystallizer operation phases considering different phenomena taking place in the system. Aamir et al. [47] proposed a hybrid model-based approach for the design and control of batch cooling crystallization operation. Through the validated population balance model, the effect of the seed recipe on the crystal size distribution (CSD) has been quantified. Therefore, desired crystal shape distributions can be predicted by identifying the optimal seed recipe for batch cooling

crystallization operation using model-based optimization [48]. Alvarez et al. [49] investigated the size distribution of crystals of different APIs in a continuous plug flow crystallization operation to evaluate the mixing effect as a function of the number of the antisolvent addition points in the crystallizer. Su et al. [50] applied a systems approach for the optimal design of antisolvent addition point in a continuous plug flow crystallizer as a function of crystal size distribution. A population balance (PBE) model was developed for the plug-flow crystallization process considering the kinetic expressions for crystal growth, nucleation, and mass balances. The process parameters were regressed using available experimental data and the model validated [49], [50]. Quon et al. [51] experimentally studied a reactive mixed suspension mixed product removal (MSMPR) crystallizer for the production of aliskiren hemifumarate. A population balance model including growth and nucleation kinetics and mass balance equation was also developed and validated. Further, the model has been used for purity and yield optimization studies of crystallization operation where the crystallizer is a part of a continuous pharmaceutical drug manufacturing pilot plant. Ferguson et al. [52] compared the performance of batch crystallizers, MSMPR, and MSMPR by incorporating a membrane, which selectively concentrates the API in the mother liquor after the first stage of the MSMPR operation during crystallization of cyclosporine. The use of a hybrid configuration improved the performance of the process in terms of yield and purity compared to the batch operation and at the same time possibilities of product contamination were minimized [52]. Zhang et al. [53], investigated the effect of the antisolvent addition on final crystal properties in a two stages MSMPR crystallizer by developing a PBE model based on the experimental data to optimize the crystal purity and yield with respect the operation conditions (temperature and residence time). The developed crystallization models have been used in many application, such as, use of predictive control of the polymorphism phenomenon during the batch crystallization operation [54], to investigate scale-up aspects of continuous and batch crystallization operation [55], and for the evaluation of batch to continuous (MSMPR) crystallization operation with respect to their design (start up, superasutration) and control [56]. In Figure 2.2, different types of crystallizers are illustrated, the traditional cooling batch crystallizer (Figure 2.2a), the plug flow crystallizer with multiple antisolvent point addition (Figure 2.2b), a two stages mixed suspension mixed product removal (MSMPR) crystallizer without recycle (Figure 2.2c) and an oscillatory baffled crystallizer.



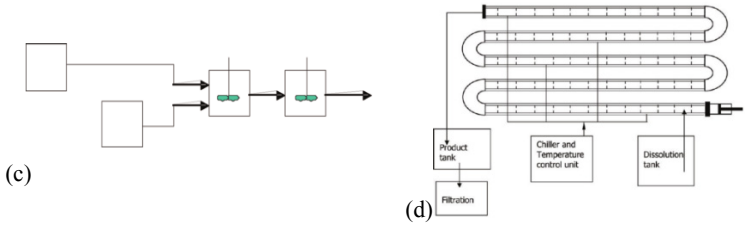


Figure 2.2 Different operational crystallzation modes published in literature. (a) Batch cooling crystallizer [46], (b) plug flow crystallizer [49], (c) mixed suspension mixed product removal (MSMPR) crystallizer without recycle [57] and (d) oscillatory baffeled crystallizer [58].

2.2.1.3 Property prediction models

Property prediction models are required for the prediction of pure compound properties and mixture properties of compounds and mixtures. For the prediction of pure compound properties, group contribution models [59], [60] are employed, while for the prediction of the VLE and LLE mixture properties UNIFAC [61] model can be used. For solubility or SLE calculations, models such as NRTL-SAC [62] and PC-SAFT [63] can be used. The thermodynamic models are important for the analysis and design of the unit operations. For example, to design a solvent-based crystallization unit, solubility calculations are needed to evaluate the crystallization performance for different solvents. Therefore, predictive models are useful for synthesis and design of pharmaceutical processes as different process alternatives can be evaluated without the need for extensive experimental work [20], [64], [65] .

2.2.2 Secondary production

2.2.2.1 Blending operation

Adam et al. has shown that high process understanding can be achieved by using discrete element method (DEM) for blending operations [66]. Boukouvala et al. investigated the blending process by using PBE/DEM and data driven models and showed that these models can be used for process synthesis, optimization and control of a continuous blending process [67]. Barrasso et al. developed a PBE model validated with experimental data for mixing operation in order to predict the quality of the final product [68].

2.2.2.2 Drying operation

The drying operation is usually performed after the wet granulation step to remove the solvent from the wet granules. The selection of the drying process can affect the properties of the powder product, such as, porosity, density and shape distribution [69]. Drying technologies are classified in terms of supply of the thermal heat to the system, such as convection, conduction and vacuum. Fluidized bed drying (convection drying technique) has been modelled as a motionless droplet consisting of two parts, a wet porous particle surrounded by a water layer at the surface and a crust region when the water has been removed from the droplet [70]. A theoretical model has been developed by Mezchericher et al. [70] and it has been used by Mortier et al. [71] for model identification/discrimination. In comparison of microwave-vacuum drying to fluidized bed drying, the granules had lower level of porosity, higher bulk and tapped density, retained the spherical shape, and the mean particle size was lower for longer

operation time. Overall the performance of these two different operation techniques is comparable [72].

2.2.2.3 Tablet compaction

Boukouvala et al. [73] developed a dynamic model for continuous pharmaceutical tablet manufacturing through a continuous wet granulation process. The total model of the process was based on a combination of mechanistic models, population balance models, empirical models and correlations along with the available process knowledge. The models, which described each operation in the process, were combined in a process line, which was simulated for different design scenarios and disturbances. Boukouvala et al. [74] conducted a model based study of continuous table manufacturing in two different cases studies: direct compaction and dry granulation. The simulation of both cases studies was coupled with sensitivity analysis to identify the important process parameters [74]. The same authors also investigated the possibility of simultaneous simulation and optimization combined with black-box feasibility analysis of the continuous tablet manufacturing with direct compaction [75].

2.2.3 Plant-wide models

Plant wide dynamics models are also necessary for the study of batch and continuous pharmaceutical processes, in order to deal with operational issues such as process evaluation for different operational scenario, solvent integration and optimization [20] start-up, shut down, changing in production lines and dealing with arising problems [26]. A plant-wide steady state model containing micro-reaction and micro-separation has been introduced by Gerogiorgis and Barton [76]. The proposed model describes a process consisting of four reactive steps and three separation steps where economics and the environmental aspect were evaluated and compared with a conventional batch process [76]. Barton et al. [16] developed a plant wide control strategy based on a plant-wide dynamic model [77] for a continuous pharmaceutical pilot plant that has been used to investigate the parametric sensitivities for the evaluation of control structures. The developed dynamic model describes the production of API in two reactors, the purification of API (liquid-liquid extraction, crystallization, reactive crystallization, wash-filtration, flash evaporator) and the production of the final drug (mixer, dilution, absorption and drying) [77]. Plant-wide steady state simulations have been performed by Jolliffe and Gerogiorgis [78], [79] to evaluate process performances of ibuprofen and artemisinin flow synthesis. The process development involves kinetic analysis, solvent selection for the purification step, and process evaluation in terms of economics [80] and environmental impact (E-factor) [78]. A dynamic plant-wide model of an integrated plant describing a purification step (API crystallization), followed by filtration and drying process, combined with a powder mixing unit has been investigated by Sen et al. [81], the analysis has shown the effect of crystallization temperature on the final tablet properties [74]. The analysis can be used to relate the critical process parameters of the primary production to the secondary production leading to improved integrated process development.

2.3 Process synthesis in pharmaceutical processes

For pharmaceutical processes, the process synthesis problem can be classified as reaction pathway identification, unit operation selection and sequence, solvent selection and process evaluation.

2.3.1 Reaction Synthesis

Organic chemistry has an important role to play in development of synthetic routes for drug development during early stage of process development. To pursue chemical research at high level, access to chemical information is needed and this can be provided by using knowledge databases, experience, literature review and/or computer-aided tools [5], [82]. The retrieved data is used for similarity search, reaction data retrieval, synthesis route planning, drug discovery and prediction of physicochemical properties [83]. The development of methods, algorithms and tools to systematize the data collection and the data retrieval of chemical information and to assist the solution to many problems related to the synthesis problem in organic chemistry has been started a long time back, around 1970s. The methods and tools for reaction synthesis are based on retrieving chemical information organized in chemical reaction databases where data for individual reactions and molecular structural information for compounds involved in the reactions are stored.

Computer-aided tools have been developed to solve problems related to "synthesis" and "retrosynthesis". The focus of these tools is to generate a number of possible chemical synthesis paths for possible precursors (synthesis tree) to achieve the synthesis of a given target compound. In retrosynthesis, the process of generating the possible pathways starts from the given target compound, and by going backwards the reactions needed to synthesize the target compound are identified. In addition, the reactions needed to produce the reactants of identified reactions are generated. The process is continued until commercial available reactants are identified. These approaches are based on heuristics and logical rules and all of them rely on knowledge databases [84]–[88]. Recently, computer-aided tools that are based on algorithmic approaches have been developed, such as The Route Designer, [10] which automatically extracts rules that capture the essence of the reactions in the chemical reaction database [89]. The tool ICSYNTH utilizes a graph-based approach with available data from literature to generate the reaction rules [90]. Many other computer-aided methods and tools for reaction synthesis have already been developed with different characteristics [89], [90]. For example, tools to perform combinatorial searches, to screen generated alternatives based on information retrieved from knowledge databases and to perform extensive reaction assessment calculations [91]–[95]

Searching for reactions and retrieving relevant information is a complex problem because it involves searching for chemical structures (complete or partial), transformation information (reaction centers), description of the reactions (reaction type, general comments) and numerical data such as experimental reaction data (including conversion, yield, selectivity, reaction conditions etc.). Reaction databases help to organize, store and retrieve data continue to be developed since the beginning of the 20th century (Houben-Weyl [96] and Theillheimer [97]). Since then, the field of reaction databases has evolved and databases such as CASREACT [98], ChemReact [97] and REAXYS (previously Beilstein plus Reactions) [99] are well-known [100].

General Databases: In this type of databases, the information included is dedicated to organic reactions and synthetic methods in general.

The CASREACT reaction database [98] started in 1840 and since then more than 74.9 million reactions have been added and it is updated daily. The information is related to organic synthesis, including organometallics, total synthesis of natural products and biocatalytic

(biotransformation) reactions. This database can be used to provide information on different ways to produce the same product (single step or multi-step reactions, uses or applications of a particular catalyst and many ways to carry out specific functional group transformations. The REAXYS reaction database [99], which is based on data from Elsevier's industry leading chemistry databases (CrossFire Beilstein, CrossFire Gmelin and Patent Chemistry Database), includes more than 40.7 million reactions from 1771 to the present. It includes a huge number of compounds (organic, inorganic and organometallic) and experimental facts (yield, solvents etc.). It is searchable for reactions, substances, formulas, medical chemistry, literature, and data such as physico-chemical data, spectra, natural product, and is searchable. Finally, the REAXYS database can be used for synthesis route planning. The Current Chemical Reaction (CCR) database [101] includes over one million organic reactions together with reaction diagrams, critical conditions and bibliographic data. The Reference library of synthetic methodology (RefLib) covers reaction data from 1946 to 1992. The database contains information from different sources and the latest version has a comprehensive heterocyclic chemistry database [97].

The ChemReact reaction database [97] is a closed database that covers time period from 1974-1998 and includes over 3.5 million reactions. It is searchable for reaction types and provides information for the reaction transformation classified by type of reaction and relevant data (bibliographic, spectra and yield). Chemogenesis is a web-book [102], dealing with chemical reactions and chemical reactivity. It examines the rich science between the periodic table and the established disciplines of inorganic and organic chemistry. The Organic Synthesis database [103], includes more than 6,000 organic reactions, and is searchable by reaction type or the structure of the compounds and it provides information for single and multi-step organic reaction together with reaction compound, conditions and description. The Reaction database-Chemical Synthesis [104] enables the user to find reactions related to reagents or target products and it also provides information with necessary details for the reagents. The Synthetic Pages reaction database [105], covers 292 reactions and provides information for the optimized reaction procedure. It is searchable by reaction type and/or the structure of the reagent or the target product. The Chemical Thesaurus reaction database [106] contains 4,000 reactions classified as organic, inorganic, organometallic, transition metal and biochemical.
The WebReaction reaction database [107] covers over 400,000 reactions, it can be searched by defining the structure of the reactant and the product and it performs search based on the reaction similarity with focus on reaction center. The Science of Synthesis database (previously Houben-Weyl) [96] contains information for organic and organometallic reactions with detailed experimental procedures, methodology evaluation and discussion of the field. Finally, the SPRESI reaction database [108] covers 4.6 million reactions and it enables searching of structures, references and reactions.
The Synthetic Reaction Updated (previously Methods in Organic Synthesis) covers many organic reactions (in graphical form) and is searchable by reaction type [109].

Specialized databases: Databases, which are specialized in one class of reaction types.

The ChemInform reaction database [100], includes more than 2 million reactions, including organic, enzymatic and microbial reactions. The available data in the database can be used for the application of new reagent and catalysts as well as for the preparation of natural and pharmaceutical products. Other aspects that are covered from the ChemInform database include synthetic procedures, enantio-and diasteroselective syntheses and new protection/de-protection procedures. The Biotage Pathfinder reaction database [110] is specialized in the verified methods for microwave synthesis.

The e-EROS (Encyclopedia of Reagents for Organic Synthesis) [111] focuses on the reagents and catalyst use in organic synthesis. The FlowReact Search [112] covers a range of over 2000 flow chemistry reactions adapted from publications on pharmaceutical, fine chemical and biotech companies. The Protecting Groups reaction database [113] provides information for the protecting, de-protection and trans-protection methods, stability, liability and reaction conditions and includes up-to-date information. Recently, a reaction library focused on generic reactions (88 reactions, ~ 20,000 reactants) with high reliability and reasonable yield has been developed by Masek et al. [114]. The objective of this library is to provide information for synthetically feasible design ideas for de novo drug design.
Representing chemical reactions in a structured way is a complex task. The reaction information contained in a database needs to fulfil several criteria and needs to be categorized with respect to their searchable reaction information. The criteria that a reaction database should fulfill are [97]:

i. **Each reactions is an individual record in the database (detailed and graphical)**

The reaction must be able to be retrieved from the database as a detailed record (reagents, products, stoichiometry etc.). It can also be extracted as a graphical representation where the reaction scheme is shown. In many databases, the reaction has been presented in a graphical form.

ii. **Structure information for target product as well as substrates**

iii. **Reaction centers**

The reaction center of a reaction is the collection of atoms and bonds that are changed during the reaction [83]

iv. **Reaction compound must be searchable**

Information for the compound involved in reactions such as reagent, catalysts, solvents etc.

v. **Multistep reactions**

In case of multistep reactions, all reactions (individual and whole pathway) must be searchable

vi. **Reaction conditions**

Conditions such as pH, temperature, pressure etc. should be searchable by exact and a suitable range of values

vii. **Reaction classification**

The type of reaction (e.g. esterification) should be searchable

viii. **Post-processing of the database contents**

Export of the retrieved reaction data in other tools (e.g.MS Excel)

In Table 2.1, existing reaction databases are listed and have been classified based on the different criteria, also the number of reactions, as well as online sources have been listed.

Table 2.1 Database review, all the databases have been summarized with respect to the number of reactions and the focus of the database. The database information has been retrieved in July 2016.

Database	Number of reaction	Criteria [97]	Reference
CASREACT	>74.9 million (1840-present)	i, iv, v, vi	[98]
REAXYS (previously CrossFire Beilstein)	40.7 million (1771-present)	i, ii, iv, vii	[99]
Theilheimer	>72200 (1946-1980)	i, v, vi, vii	[115]
ChemInform RX	>2 million (since 1990-present)	i, iv, vi,	[100]
Current Chemical reactions	1,083,758 (1840-present)	i, vi	[101]
Methods in Organic synthesis	33,000 (1999-2014)	i, vii	[109]

Reference library of synthetic methodology	209.800 (1946-2001)	i	[97]
ChemReact	3.5 million reactions (1974-1998)	i, vii	[97]
Chemogenesis	-	ii, iii	[102]
Organic synthesis	>6000 (1921-present)	i, ii, v, vi, vii	[103]
Reaction Database-Chemical Synthesis	-	i, ii,	[104]
Synthetic Pages	292	i, ii, vi, vii	[105]
The chemical thesaurus	4,000	i, ii	[106]
WebReactions	>400,000	i, ii, iii	[107]
Biotage Pathfinder	>1,000	i, vi, vii, viii (reaction assisted with microwave technology)	[110]
e-EROS Encyclopedia of Reagents for Organic Synthesis	>70,000 (4,000*)	i, ii	[111]
FlowReact Search	>2000	i (reaction in flow)	[112]
Protecting groups	-	i	[113]
Science of Synthesis (previously Houben-Weyl)	240,000 (early 1800s-present)	i, ii, iii	[96]
SPRESI	4.6 million	i, ii, iii	[108]

Many reaction databases have been developed over time, some of them have a large number of reactions available and others smaller number; some of the databases cover the whole range of the organic and/or inorganic reactions; but also there are reaction databases that cover additional specialized reactions such as solid reactions, flow reaction etc. It can also be seen, that most of the databases cover the most important criteria as they have been defined by Zass [97] such as the need for individual reaction records (criterion i, in Table 2.1) and other criteria.

2.3.2 Unit operation selection and sequence

For the development of pharmaceutical processes, decisions in the early stage of their development that establish an appropriate synthetic route for an API is an important feature for industrial-scale process [5]. However, once the synthesis route has been established and reaction optimization has been performed, the type and the sequence of unit operations have to be determined for efficient production of the APIs. Not many studies in the literature are dealing with the generation of separation alternatives in pharmaceutical processes as the focus is usually on the synthesis pathway development. However, many studies have been published dealing with improvements on separation techniques for certain mixtures. Recently, Cervera-Pardell et al. [116], proposed a framework based on PSE methods and tools to retrofit batch pharmaceutical processes and to convert them to the continuous mode with special emphasis on solvent selection, reactor design and separation processes. In this study, a liquid-liquid separation operation of a biphasic mixture was replaced by a hydrophobic membrane, which demonstrated better process performance. The membrane operation indicated that the driving

force for the separation is based on surface tension. Therefore, by the use of the identified membrane it was possible to separate two phases continuously and to reduce the number of the unit operations. A solvent exchange, a solvent-based crystallization and a drying operation were avoided due to the improved liquid-liquid separation [13]. A synthesis tool for separation processes based on heuristics and simulation information developed by Morao et al., was used to generate separation alternatives for the purification of an API [117]. Wong et al. [118] summarized the design approaches for continuous cooling crystallization processes with recycle for cyclosporine and a continuous antisolvent-cooling crystallization process for deferasirox. A continuous crystallization model based flow-sheet was simulated by Hsieh et al. in order to reduce the mean size of API crystals [119]. Moreover, the recovery of isoflavones via absorption and membrane-based separation was simulated by Kawachale et al. [120]. The simulations were based on published experimental data and different scenarios were tested and economic evaluation was performed for each scenario [120]. The purification of API and the mixing with the excipient(s) was investigated by Sen et al., the operations: crystallization, filtration, drying, and mixing represented the process. DEM and PBM were coupled in order to describe the process, and the process was optimized in order to identify the optimal operation conditions [81], [121]. Synthesis of a batch process for tablet manufacturing was also studied by Papavasileiou et al. [122].

2.3.3 Solvent Selection

Pharmaceutical products are usually produced via multistep organic reactions where in most cases the use of solvents is required to improve the reaction efficiency [123] and to assist with separation and final purification of the product [7]. The importance of solvent selection for multistep organic reaction systems for greener manufacturing is indicated by Foli et al. [124] and Gani et al. [125] where reaction tasks are employed to convert specific raw materials to desired products (for example, active ingredients or intermediates) through defined reactions. Solvents have an important role to play in reaction tasks as they can promote the reactions in terms of yield, selectivity, and mass efficiency. For example, solvents can serve as reaction mediums, as carriers for the solute, as creators of phase splits, as cooling/heating agents [126]. Solvents are also usually employed for the purification and recovery steps of the APIs (crystallization task). Here also, solvents have an important role to play as the selection of an appropriate solvent can define the success of the crystallization task. For example, solvents can be made to affect the solid solubility curves such that the product recovery is increased [127] or to obtain the shape of the solid crystals [128]–[130]. The extraction tasks are usually performed after a single-phase reaction task when two phases are created by the addition of a solvent to separate a product from the reactants or to recover the product from another solvent in cases of temperature sensitive solutes. Therefore, solvents are used in the extraction tasks to enhance the partitioning of compounds between two phases and thereby increase the product yield. Finally, the washing tasks are applied to remove water-soluble impurities (e.g. salts). Here solvents that can dissolve the solute but are immiscible with water are used to trigger a phase split with an aqueous (reaction) phase.

A general systematic procedure for solvent selection to identify solvents for different unit operations has been proposed by Gani et al. [17].

2.3.4 Process Evaluation

Energy optimization during early stage design has been highlighted by Jimenez-Gonzalez and Overcash [14] by demonstrating the potential benefits on the operating cost and environmental impact during early stage design of the process to produce steraline. The process to produce the steraline consists of four steps and two steps using different solvents were considered [14]. Economic analysis of a batch and alternative continuous processes for the production of an API in pilot scale was performed by Schaber et al. [131]. The economic analysis was based on different scenarios including intermediate cost, different configuration of the continuous process, recycle loops and different ways for tablet compaction (roller or direct). The economic analysis had shown that in most of the cases, continuous processing is more profitable (up to 44% depending on the operational scenario) compared to batch process [131].

Sustainability evaluation must be performed during early stages of process development [132] and before the approval of the regulatory bodies as the re-approval of the process can be a very expensive process [116]. Constable et al. [133] reviewed the possible use of "green" metrics in order to enhance the awareness of the generated wastes from reaction and to identify opportunities for further improvement.

Recently, life cycle assessment (LCA) for evaluation of the environmental aspects of pharmaceutical processes and identification of optimization and intensification targets have been used for pharmaceutical processes. Kressirer et al. [134] investigated the green process design for Kolbe-Schmitt synthesis using life cycle assessment. The authors considered many process alternatives including different energy sources, process conditions, reactive media, operation modes, and work up techniques[134]. Ott et al. [135] investigated an API process at Sanofi, which involves, two reactions, filtration, washing, a solvent swap and drying operations. The authors considered different batch and continuous processing alternatives based on optimization targets identified by analysis of the base case. Similar to their previous work, Ott et al. [24] have performed life cycle assessment comparing different reaction pathways for the synthesis of Rufinamide and demonstrated that process improvements are achieved by implementation of continuous manufacturing and solvent integration. Recently, Theoh et al. [136] evaluated a pharmaceutical process that involves a two-phase reactive system considering three alternatives for the final separation step: a solid-liquid batch operation, a liquid-liquid batch operation, and a liquid-liquid continuous operation [136]. The process alternatives have been evaluated through experimental procedures and compared in terms of several performance criteria such as raw material consumption, waste generation, energy requirements, capital and operation cost. It was concluded that continuous processing has demonstrated higher energy efficiency, lower VOC emission, better volume efficiency, smaller processing inventory, smaller equipment footprint, lower product loss through waste and lower operating cost [136].

The development of sustainable greener processes is a challenge for pharmaceutical industries [8, 66]. The use of biocatalysis and biotechnology for the production of pharmaceutical products seems to be promising [134], [138]. Biosynthetic production of insulin was investigated by Petrides et al. [139], batch process was developed following the principles of conceptual process design, the process was economically evaluated and a sensitivity analysis was performed. Process considerations for the asymmetric synthesis of chiral amines via bio-catalysis were recently reviewed by Tufvesson et al. [40]. Chiral amines are widely used as building block for pharmaceuticals (APIs and NCEs) and they can be produced by chemical

and biocatalytic synthesis, however the chemical routes are not efficient enough. On the other hand, the biocatalytic synthesis has gained much attention, and the authors describe the process, identify the process challenges and describe the strategies used to overcome these challenges and describes the thermodynamic, biocatalyst, solubility limitations [40]. Carbamazepine (API) crystals were produced via electro-spraying for continuous manufacturing, the study shows that the electrospray technology can help in the intensification of pharmaceutical processes and it might be able to produce pharmaceutical dosage forms [140]. The concept of microfluids was applied by Benasker et al. [141] in order to produce fine chemicals (2 cases studies – chemicals produced by batch processes). Different scenarios were tested experimentally and an economic evaluation was performed for each one to identify the most economical feasible configuration [141].

2.4 Batch to continuous processing

The advantages of continuous manufacturing against batch manufacturing had been extensively reviewed by several authors [9]. Several examples of converting batch processes to continuous manufacturing have been published and they can be classified in terms of three research areas: APIs synthesis, purification of APIs, downstream processes to produce the final form of the drug.

Cervera-Pardell et al. [15] demonstrated the use of a systematic approach how to retrofit a batch process for production of API into a continuous process. The study emphasized the importance of solvent selection and replacement, reactor design and separation process design. The systematic framework guides the process developer to follow a step-by-step procedure that also provides the necessary information and the associated methods/tools for decision-making in the early stages of process design [15]. The obtained process is then evaluated with respect to its efficiency, time, cost, and environmental factors. Then the process can be optimized and intensified in order to reduce the cost, the manufacturing time and to increase the productivity and the final process flowsheets can be validated either through experiments or simulations. Cervera-Pardell et al. converted partially a batch process for the production of an API (Zuchlopentixol) to a continuous process [15]. The synthesis pathway consists of four reactive steps, a Grignard reaction, a hydrolysis step followed by liquid –liquid extraction, then solvent swap from THF to ethanol/water mixture, a crystallization step followed by drying, a hydration reactive step, and finally a hydroamination step. The first reactive step was successfully converted to a continuous process using a continuous filter reaction [142], [143] to separate the formed solids from the liquid reaction mixture. A tubular reactor was used together with a liquid-liquid membrane separation to replace the batch reaction and the batch liquid-liquid separation. The use of the membrane made it possible to improve the separation performance and obtain an organic phase, which does not need further separation/purification [13]. By using the membrane operation, the unit operation reduced by three: a solvent swap operation, a crystallization operation and a drying operation [15] were no longer needed. The 3rd reactive step was accelerated by optimizing the reaction conditions through a kinetic study and converted to flow reactor [144]. The final reactive step was accelerated by performing kinetic analysis in solvent-free environment and by optimizing the reaction temperature and stoichiometry. After the kinetic analysis, the reaction was completed in 4hr instead of 24hr [10]. The hydroamination reaction (4th step) was also accelerated using microwave assisted organic synthesis resulting in slightly better reaction performance, although the capital and operating

cost of microwave equipment is too high [10]. The final process design was validated by experiments [116], [10].

Mascia et al. [145] presented a fully integrated continuous manufacturing plant for the production of a pharmaceutical product (API: aliskiren hemifumarate). The integrated continuous process contains lower number of unit operations compared to the conventional batch process and the overall residence time was one order of magnitude lower in the continuous process (47hr) than in the traditional batch-wise process (300 hr) [145]. The process integrates the chemical synthesis, purification, formulation and tableting steps, and, the product quality was maintained by using an automated control system [145].

Laporte et al. [12] reported the conversion of 6-Hydroxybuspirone from batch to continuous manufacturing. The reaction consists of two steps, a deprotonation step where an enolate is formed, and an oxidation step where the 6-hydroxybuspirone is formed. The main driving force to convert the batch reaction system to continuous was the extremely low temperatures required for the safe operation and high reaction performance. The reaction is taken place at temperature below <-25^{o}C as the intermediate product degrades fast in temperatures above the -25^{o}C. The main concern was that the oxidation step is moderate exothermic and it might increase the adiabatic temperature by 68^{o}C, which might be dangerous during the operation as a flammable solvent and oxygen are involved. A solution to minimize the potential process risks was to use a microreactor for the oxidation step because of smaller hold up times, and more efficient heat removal. Single-stage and two-stages microreactors were evaluated resulting in conversions of 65-70% in 2-3min and 85-92% in 5-6min. The productivity of the system was not suitable for the scale up [12]. Another system, involving an enolation continuous reactor and counter-current flow trickled bed reactor was used resulting in higher conversions and lower residence times (1 min and 3.5-4 min, respectively). The process was operated in lower temperature increasing the process safety and it was possible to scale up by numbering up [12].

A continuous trickled-bed reactor was also used by Shen et al. [146] to convert the batch dehydrogenation of tetrahydrocarbazole in continuous operation. Continuous synthesis was enabled in many cases by modifying the chemistry of the pathway (Ibuprofen [147], [148]), and using microfluid technologies or by introducing new technologies (photochemical transformation, Artemisinin [149]). Many other reaction systems have been used to convert batch to continuous reaction systems such as membrane reactors for Heck reaction [150] and transamination reactions [151]–[153], fixed bed catalytic reactors for amination reactions [154], continuous microreactor for protection reactions [155], azide synthesis reactions [156] and synthesis oxindoles reactions[157].

Mixed suspension mixed product removal (MSMPR) crystallizer [53], [56], [118], [158]–[160], oscillatory baffled crystallizer [58], [161], [162] and plug flow crystallizer [49], [50] have been mainly used to convert batch crystallization operations to continuous one.

2.5 Conclusions

2.5.1 Synthesis route

The pharmaceutical process development starts with the selection and development of the synthesis route to produce high quality active pharmaceutical ingredients (APIs) that is environmental benign, economic viable and has high product yield. The design of the synthesis

routes, usually starts from a given target compound and by going backwards, reactions are generated until commercially available compounds are identified (retrosynthesis). To assist the chemical synthesis problem, detailed reaction databases and computer-aided tools are required to create a data-rich environment. With detailed information for different processes available, the procedure to identify and optimize the reaction route becomes faster. In addition, process knowledge assists with troubleshooting during the development. The connection to parameters such as reaction conditions, experimental data and models of criteria like scalability, cost, expected yield, green chemistry metrics [133], number of reaction steps, easy of separation, safety, can further improve the process understanding and the decision making process.

2.5.2 Reaction analysis/improvement

The core of any pharmaceutical process development is the complex chemical transformation under specified conditions lead in the synthesis of the active ingredients from commercially available compounds. Therefore, the improvement of the individual reactive step is important for the overall process performance as it can reduce the operation time, the required separation steps, the complexity of the separation steps, the environmental impact and the overall operating costs. Different designs (e.g. solvent, solvent role), technologies (e.g. microwaves), reactor types (continuous/batch) and operation conditions (e.g. P, T) can be evaluated using kinetic studies (experimental- and/or model-based methods) and to assist the decision making process such as selection of reaction conditions and operation mode.

2.5.3 Separation analysis/improvement

Improvements in the separation process can lead to significant improvements in the operational time, mass and energy intensity, the number of unit operations, the operational cost, and the environmental impact. Analysis of the mixture to be separated based on thermodynamic insights to identify the separation tasks with the maximum driving force and to determine the separation sequence [163],[164] is required. Mixture analysis using detailed thermodynamic models is necessary to obtain the separation factors, determine the operating conditions and finally, to evaluate the process performance of different generated separation alternatives using model-based or experimental methods.

2.5.4 Batch to continuous

Batch-wise processes are multipurpose and flexible operation, and allow analysing the product quality at discrete times. However, as it has been discussed above, implementation of continuous manufacturing might be highly beneficial for the overall process performance as it might reduce the potential risks, increase the volume process productivity and improve the performance of unit operations in terms of time, operation cost, and resources. In pharmaceutical processes, the reaction and the purification (crystallization) operations are often operated in a batch mode due to slow reactions and high residence times. Therefore, reaction and crystallization operations should be analysed in a way to investigate whether or not a continuous operation is beneficial and feasible and finally propose a continuous design that might be feasible. Then mechanistic dynamic models or experimental studies should be performed to investigate the viability of the proposed designs, to evaluate the overall operation including startups and the shutdowns and finally propose an efficient control strategy.

2.5.5 Solvent selection

In pharmaceutical processes, solvents have a multipurpose role since different solvents can be used in different processing steps, such as chemical reactions, separation and purification, during synthesis of active pharmaceutical ingredients (APIs), including its purification/isolation. The solvent selection for the individual synthesis, multistep reaction steps and separation/purification steps has been widely investigated in literature. In pharmaceutical processes, very often, a reaction may take place in solvent-1 (S1) and the next processing step (e.g. reaction, crystallization, extraction, or washing) may require a different solvent-2 (S2) because the process performance is better in S2 than in S1. Therefore, solvent swap (or solvent exchange) is a common and important task in API production line within pharmaceutical industry. The solvent selection and analysis for the individual processing operation have already been well defined and established by Gani et al. [17], however, a method for solvent selection of swap solvents and analysis of their performance has not yet been proposed.

2.5.6 Process evaluation

The main driving force of pharmaceutical process development is the production of products in high purity and high yields, although, process evaluation with respect to energy consumption [14], evaluation of environmental metrics [133], life cycle assessment [24], [135] has only been applied, to our knowledge, in few examples [136]. The integration of process evaluation methods during early pharmaceutical process development different alternatives related to the potential synthesis routes, solvent use, operation modes, process flowsheets (or state-task networks) and different designs of unit operations can be evaluated. Optimization targets can be identified and optimization studies can be performed in a systematic manner. Despite the overall process improvement, which can be achieved through evaluation of different operational scenarios of a particular process, process evaluation needs to be performed at the early stages before the process approval from the regulatory bodies as the re-approval of a modified process can be an expensive process.

3 FRAMEWORK FOR PHARMACEUTICAL PROCESS DEVELOPMENT: METHODOLOGY

In this chapter, the overall integrated framework is presented, highlighting the main objectives and the main steps needed for application of the framework. Secondly, the detailed work- and data-flows are presented and, finally, each step of the framework is explained in detail.

3.1 Framework objective

The objective of the proposed framework is to assist in the development of pharmaceutical processes by providing detailed process understanding and identifying opportunities where continuous manufacturing might be an option. The developed framework aims at improvements in the following areas: reaction pathway selection, reaction analysis, separation synthesis, and finally, process simulation/evaluation and optimization. Systematic model-based methods and tools are applied in each step of the framework in order to create a data-rich environment that is a requirement for enhanced process understanding and finally, [5] to assist in the decision making process in each case. The expected outcome of this framework is a sustainable process with high product quality and low risk within a design space. An overview of the developed framework is illustrated in Figure 3.1

3.2 Framework architecture

The framework (Figure 3.1) follows the process development cycle during the early stage of drug and process development. It is based on systematically efficient acquisition of process knowledge that is generated by the use of systematic model-based methods and tools to provide complementary data to the experimental data and/or to assist the experimental studies when they are necessary. The developed framework focuses on the process development/improvement for the production of small molecules active pharmaceutical ingredients (APIs). The process flowsheet (or state-task network) can be developed for new APIs where information about the production process is unknown or for APIs that have produced before with known or unknown process flowsheet (or state-task network).

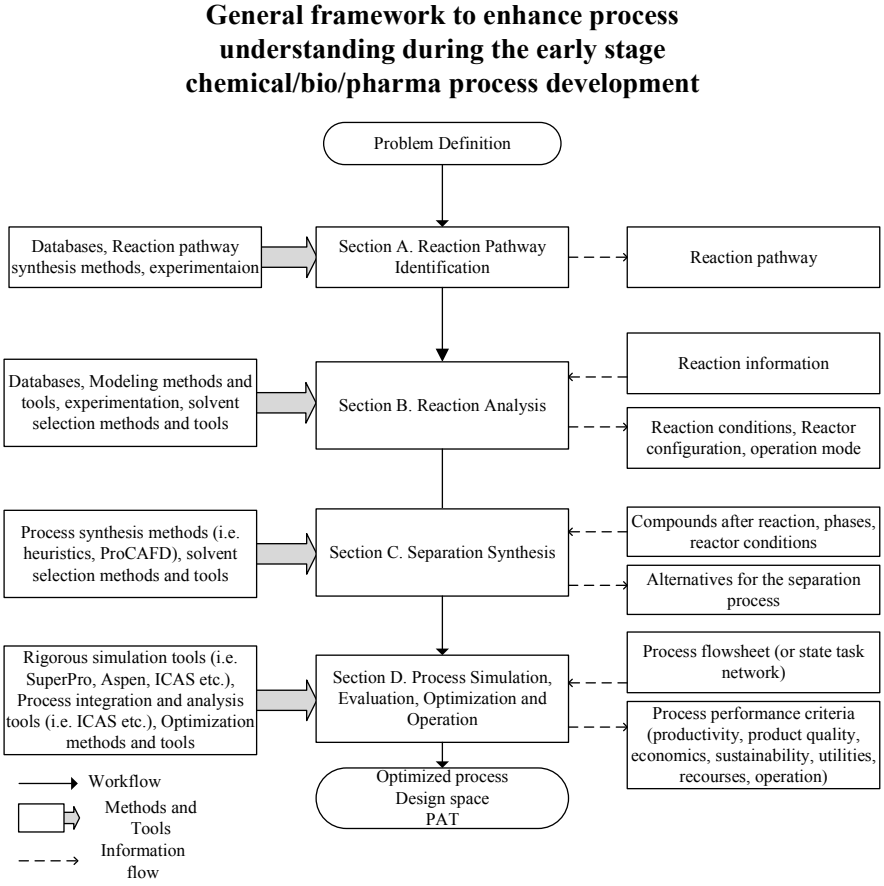


Figure 3.1 Integrated systematic framework to assist the pharmaceutical process development.

3.3 Work-flow and data-flow

Here, the work-flow and the data-flow for each section of the framework are presented and explained. The presentation of each section is given as follows:

1. The overall objective of the section and the reasoning why the specific section is needed.
2. The objective of each step for each section and the reasoning why the step is needed.
3. The required data for each step.
4. The generated information after successful implementation of the specific step of the framework.
5. The methods and tools that are required to generate information are explained.

3.3.1 Section A: Reaction pathway

Section Objective: To identify, to design or to propose a reaction pathway that can be used to synthesise the desired product (API or an intermediate).

The reaction pathway is the core of the process development for the pharmaceutical processes as it can affect important criteria for the manufacturing process in terms of scalability, production time, ease of manufacturing, produced waste, product quality, yield, and cost. The detailed work-flow of the section A is illustrated in Figure 3.2.

Step A.1. Select API or intermediate

Step Objective: To identify the compound of interest.

For known compounds, the name and the molecular structure is to be provided, for unknown compounds, the molecular structure with the necessary functional groups need to be provided.

Step A.2. Reaction synthesis pathway

Step Objective: To identify the reaction pathway.

During the development of the synthetic routes for the production of an API, chemical information is needed which can be provided by reaction databases, experience, literature and/or computer-aided tools [5]. The obtained information is used for similarity searching, reaction retrieval, synthesis route planning, drug discovery and prediction of physicochemical properties [83]. The chemical information is organized in chemical reaction databases where information for individual reactions and structural information for different component involved in reaction is available. An early evaluation of sustainability metrics [165] (see Table 4.7), process performance in terms of yield, cost, scalability [12] and/or life cycle assessment [24] can be used for the selection of the chemical route.

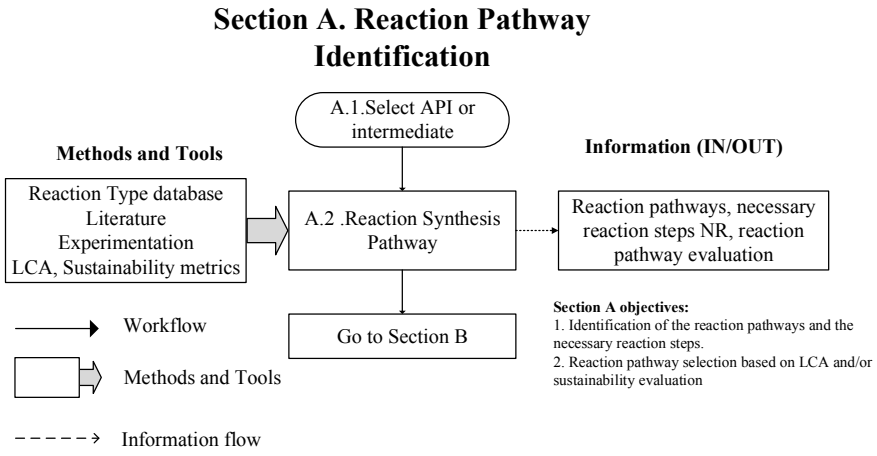


Figure 3.2 Work-flow, methods and tools and data flow corresponding to Section A for the reaction pathway identification.

Required Data: Selected compound to be produced (information obtained from Step A.1.)

Information obtained: Reaction pathway, Reaction pathway evaluation

Methods and Tools: Reaction database, literature review, experimentation, LCA tools, and sustainability metrics (see Table 4.7).

3.3.2 Section B: Reaction analysis

Section objective: To perform reaction analysis for each reaction step in order to enhance the reaction understanding and improve the individual reaction performance, to investigate possibilities of performing the reaction in continuous mode, to propose the design of the reactive system and to define the objectives of the separation if needed (Section B is illustrated in Figure 3.3).

Step B.1. Reaction data collection

Step objective: To collect all the relevant reaction data in terms of reaction type, compounds involved in reaction (e.g. reactants, products, and catalyst), reaction phases and solvent use and role, reaction conditions, available data and models, and scale.

The data is collected to preliminary investigate the compound and the reaction conditions where the reaction performance is high. In this step, the solvent role in reaction step is investigated in terms of reaction improvements such as productivity, operation time, or post-processing. Available data (e.g. experimental points, dynamic data, and kinetic models) are collected to be used later to enhance the understanding of the reaction by associating the changes in the variables with the reaction performance.

Required Data: Reactions

Information obtained: Reaction compounds (e.g. reactants, catalyst, solvents etc.), reaction products, available experimental data.

Methods and Tools: Reaction type database, experimentation.

Step B.2. Perform Kinetic Study

Step Objective: To identify mass and heat transfer limitations, reaction control mechanism, and kinetic model.

Reactions often have limitations such as heat and mass transfer limitation or equilibrium limitations. The identification of these limitation help to improve the reaction understanding and to identify possible challenges for further improvement of the reaction performance. In this step, a kinetic model, if available, can also be used to fit and validate experimental measurements. The kinetic model is often retrieved from a model library, but it can also be developed considering the phenomena taking place and available experimental data.

Required Data: Reaction information.

Information obtained: Mass and heat transfer limitations, Reaction class, and Reaction control mechanism, kinetic model.

Methods and Tools: Reaction type database, Roberge et al. [166] reaction classification, model libraries, modelling methods and tools.

Step B.3. Evaluate reaction variables

Step objective: To evaluate and identify the reaction variables such as temperature, pressure, stoichiometry, solvent, which might improve the reaction performance in terms of product selectivity, yield, conversion, reaction time, and byproduct formation.

The reaction variables can be evaluated for different operational scenario. Validated kinetic models or experimentation procedures are employed for collecting necessary data and understanding the effect of reaction variables to the reaction performance. The solvent use is also evaluated in this step, where an optimal solvent can be selected based on the desired properties using the solvent selection methods developed by Gani et al. [17].

Methods and tools: Reaction type database, kinetic models, model libraries, model development methods, experimentation, design of experiments and solvent selection/analysis and design methods and tools.

Required data: Reaction models, kinetic model, experimental data.

Information obtained: Reaction conditions, yield, conversion, selectivity, reaction time (or residence time), solvent and impurities.

Step B.4. Batch or continuous operation?

Step objective: Investigate opportunities for continuous operation.

In this step, an evaluation based on the information obtained in steps B.1-B.3 is performed to identify possibilities for reaction operation in continuous mode. Information obtained for the reaction limitations during the implementation of step B.2, together with the reaction evaluation results obtained from step B.3 and available knowledge is utilized to investigate possibilities for continuous operation.

Methods and tools: Unit operation database.

Required data: Reaction information, mass and heat transfer limitations, kinetics and reaction concerns.

Information obtained: Benefits of continuous mode, and decisions.

Step B.5. Reactor design

Step objective: To provide the reactor design

The reactor design is a function of the reactor type that has been decided to be used in step B.4, for example, if batch reactor has been selected, the volume of the reactor based on the reaction conditions to achieve the desired reaction performance is to be calculated. Other concerns such as safety, product quality, material, controllability must be also considered in this step. Opportunities for process intensification such as combination of reaction and separation are investigated and proposed in this step as well. Process intensification for reaction-separation systems has been widely applied in industry in the form of reactive distillation, multiphase reaction systems with in situ product or by-product removal or controlled released reactants in the multiphase reactors, multiphase membrane reactors and multiphase prevaporation reactors.

Methods and Tools: Unit operation database, solvent analysis tools, reactor design methods, attainable region concepts.

Required Data: Solvent screening, how separation affects the equilibrium, reaction conditions, and productivity.

Information obtained: Reactor design, opportunities for process intensification or hybrid operation

Step B.6. Is separation required?

Step objective: To define the objectives of the separation in case that separation is needed after a reaction.

The last step of the section B is to perform an evaluation on whether a separation of the main reaction product of the specific step (when NR<total reaction steps) is required or not for each step. First, all the information from the Steps B.1-B.5 is collected for each step, then, the reaction mixtures are analyzed in terms of compounds (e.g. reactants, catalyst). Then process synthesis rules are applied, for example, if the conversion of the reactant of the reaction step 1 is not complete and this reactant is inert for the next reaction step then separation of the reactant is not needed. Another concern in pharmaceutical processes, is that different solvents might be used for different reaction tasks. In the case of reaction in series where solvent 1 (S1) is required for the reaction step 1 and another solvent (solvent 2, S2) is required (because S1 is not performing well) for the second reaction step, solvent 1 needs to be removed and replaced with solvent 2, therefore, a solvent swap operation is needed to remove S1 and replace it with S2. Another consideration has to do with the possibility of recycling the unreacted raw materials, catalyst or solvent. In this case, it is required to make sure that product contamination is not possible and the quality of the product remains high.

Required Data: Information obtained from the previous steps.

Information obtained: Separation objectives

The overall outcome of the reaction analysis section B is illustrated in Figure 3.3 where the reaction compound, the reaction operation, and the objectives of the separation are shown.

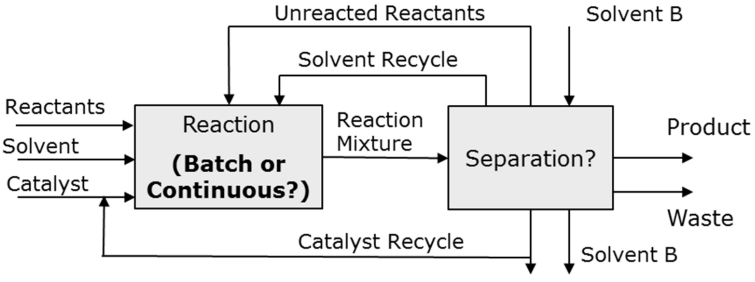


Figure 3.3 Information obtained from the succesful implementation of Section B.

In Figure 3.4, the detailed work-flow, data-flow and methods and tools required for the implementation of the Section B are illustrated in detail.

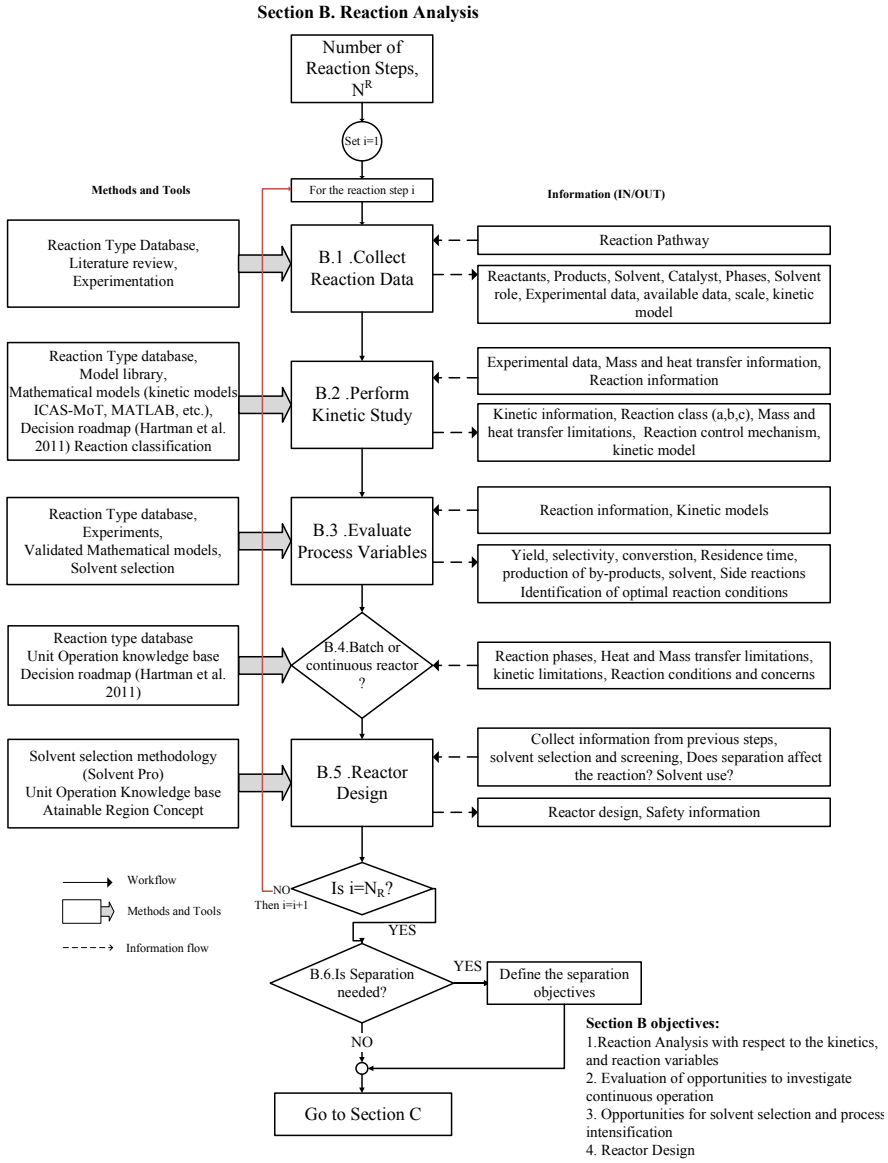


Figure 3.4 Work-flow, methods and tools and data flow corresponding to Section B for the reaction analysis.

3.3.3 Section C. Separation Synthesis

Section objective: To determine the type, the sequence and design of the unit operations that are required to satisfy the separation objectives, defined in Step B.6 (see Figure 3.3).

The complexity of the work-up and the final purification is related to the compounds present in the final reaction mixture, for example, when the amount of the side-product is low then the work-up might be less energy demanding or fewer unit operations might be required. The selection of proper separation tasks might improve the process in terms of total unit operations needed, minimization of solvent requirement, lower operational costs, and better sustainability performance. In addition, due to the complexity of the main product, operational limitations have to be taken into account in order to define the design space of the unit operations.

Step C.1. Mixture analysis

Step objective: Analysis of all the compounds present in the mixture to be separated. Separation tasks identification.

The objective here is to collect all the required information for the identification of the feasible separation tasks that can be used in order to satisfy the separation objectives after the specific reaction task. First, the molecular structures of the organic compounds involved in reaction mixture are collected. Pure compound and mixture properties are collected using databases or property prediction methods (ICAS-ProPred). Finally, the feasible separation tasks are identified as it has been proposed by Jaksland et al. (1996) [163] and by Tula et al. [164].

Required data: Compound, Separation objectives, pure compound and mixture properties.

Information obtained: Binary ratio matrix, azeotropic information, separation tasks.

Methods and tools: ICAS platform (CAPEC database, ProPred, AzeoPro), Process synthesis methods [163], [164].

Step C.2 Generate separation alternatives

Step objective: Determine the sequence of the unit operations and generate process alternatives.

After the analysis of the systems in step C.1, the sequence of the separation unit operations can be determined by combining the obtained information, with heuristics for process synthesis and driving force principles together with the objectives defined for the specific mixture to be separated. The result of this step is the generation of separation alternatives that can achieve the objectives, and they are represented as SFILES ,which is a text string representation of the process flowsheet or state task network [167].

Required data: Separation tasks, process information related to the specific case.

Information obtained: Process alternatives for the achievement of the separation alternatives.

Methods and tools: Driving force principles [168], Process synthesis methods [163], [164], literature.

Step C.3. Separation process selection

Step objective: Selection of the most promising alternatives.

After the generation of the process alternatives to achieve the separation objectives, the most promising alternatives are to be selected for further analysis. The main concern is the high yield and purity of the product and additional concerns might be required energy, number of unit operations, process safety and operation time.

Required data: Process alternatives, criteria to rank alternatives.

Information obtained: A feasible number of process alternatives that satisfy the constrains.

Methods and tools: Process evaluation tools, indexes to rank the alternatives based on predefined criteria.

Step C.4. Unit operation specification

Step objective: To analyse the unit operations of a specific flowsheet.

In this step, the separation factor and the conditions of the separation are to be identified. For separations which are based on phase creation (e.g. vapour-liquid), the corresponding phase diagram (VLE) should be analysed to obtain the recovery factors. Additionally, in this step solvent selection should be performed for the identified solvent-based separation tasks. If the solvent for separation is different from the solvent in the reaction, then a solvent swap operation is needed. The main aim of the solvent swap method is to identify the swap solvent that is suitable for the swap operation and the subsequent separation task and at the same time, key performance criteria such as operation time, solvent use, and generated waste are low. In the case that the reaction is solvent free, the solvent is selected using the well-established methods proposed by Gani et al. [17].

Required data: Phase equilibrium, process flowsheet (or state-task network).

Information obtained: Separation factors, Process conditions, solvents.

Methods and tools: Solvent selection methods, Solvent swap method, Thermodynamic models.

Step C.5. Batch or continuous ?

Step objective: Gathering all the information from the previous steps and in corporation with the decisions taken during the reaction analysis steps (Section B), a decision on whether the unit operations of the separation process can be operated in batch or continuous mode is made. In general, most of the unit operation involved during the work-up in pharmaceutical processes such as distillation, liquid extraction and membranes are compatible in continuous or semi-continuous mode [7]. The crystallization step, determines the final product quality and purity, it is usually followed by filtration, and drying and they are usually operated in batch or semi-batch mode. However, different types of continuous crystallization operations have been recently published [49], [53], [58].

Required data: Information from previous steps.

Information obtained: Batch or continuous operation.

Methods and tools: Unit operation database.

Step C.6. Design of the unit operation

Step objective: The last step is the design of the specific unit operation, in this step all the design parameters need to be specified/calculated such as the volume of the crystallizer and the amount of the solvent required to achieve the separation.

Required data: Design parameters, operating parameters, solvent, phase diagrams.

Information obtained: Design of unit operations.

Methods and tools: Unit operation database, solvent analysis tools.

The expected outcome of the section C is illustrated Figure 3.5 where is shown the reaction mixture to be separate, the separation task identification, the ranking of the process alternatives and the state task network.

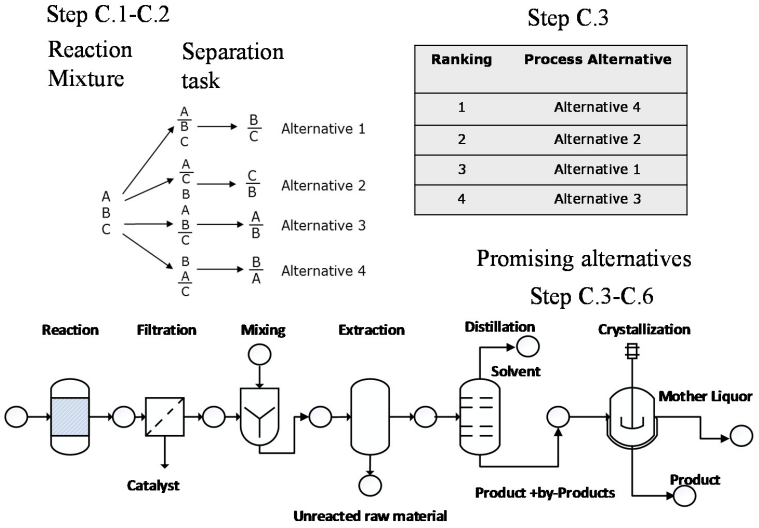


Figure 3.5 Expected outcome through the analysis in section C.

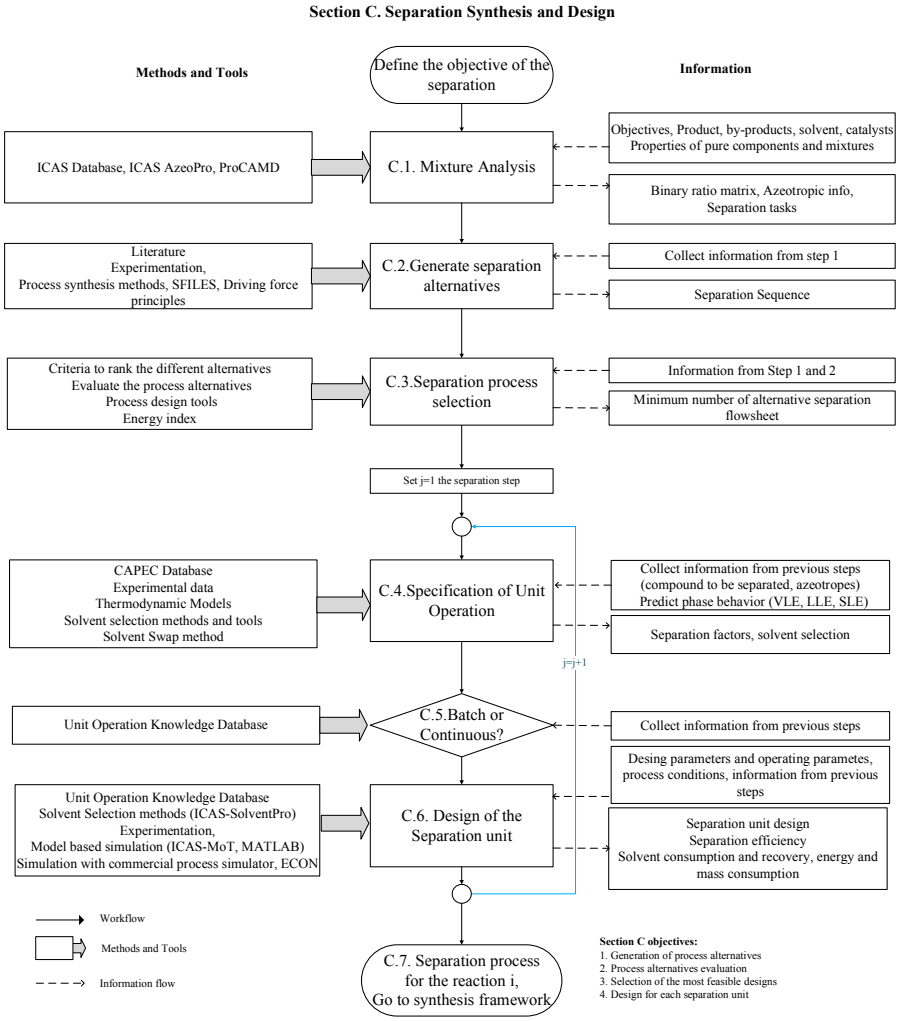


Figure 3.6 Work-flow, methods and tools and data flow corresponding to section C for the separation synthesis and analysis.

3.3.4 Section D. Process Evaluation

Section objective: To evaluate the obtained process flowsheet (or state task network) with respect to predefined performance criteria and identify targets for further process optimization and improvement. This section deals with issues like scale up/out, process intensification, process integration, process control, and implementation of monitoring and control strategies and process operation.

Step D.1. Process simulation and evaluation

Step objective: To simulate and evaluated the obtained process

Using the obtained process flowsheet (or state-task network) and all the information obtained during the analysis such as operation conditions, reaction information and separation factors, process simulation can be performed by using model-based methods (e.g. simple mass & energy balances, or rigorous models) or experimental-based methods. Performance criteria such as process efficiency (e.g. in terms of yield or operation time), product purity, productivity, energy required and solvent consumption are calculated in order to evaluate the process. In addition, process analysis is performed to identify possible opportunities (e.g. high energy or mass use) for process improvement. For example, environmental metrics to calculate the impact of the produced waste such as the toxicity into the environment are calculated using the WAR algorithm. Based on the results and depending on the source of the impact, a target for optimization can be defined, for example, when the impact from the purge of the recycle to the reactor is high, it might be an indication that reaction optimization needs to be performed. Sustainability analysis can also be performed to identify parts of the process where the utilization of energy or mass is high and translate this into optimization targets. Finally, LCA analysis can also be performed to analyse and evaluate the environmental impact of the whole process, from the extraction of raw materials to its end-of-life. In this way, the environmental impacts, from the selection of the synthesis routes, to the selection of unit operation or to the selection of the product distribution to the market can be well understood and be subject of process optimization.

Required data: Process flowsheet (or state-task network), operating parameters, design parameters and process conditions.

Information obtained: Mass and energy balances, Performance criteria, Sustainability metrics (see Table 4.7), economics, environmental impact.

Methods and tools: Rigorous model-based simulation tools (ASPEN, SuperPro, ICAS, Dynochem), dynamic plant-wide models, analysis tools (ECON, SustainPro, LCSoft).

Step D.2. Process optimization/control/monitoring and validation

Step objective: Perform optimization, establish control and monitoring strategy, and validate the process.

Process optimization is defined and performed to satisfy the optimization targets identified from Step D.1 and to improve the overall performance of the developed process. One possibility for process optimization in pharmaceutical processes is solvent recycle and integration, where high purity solvents are required in order to avoid any possibility of product contamination. The solvent recovery system within pharmaceutical processes implies high operating costs which in most of the cases leads to solutions such as discharging as a waste the used solvents during the production of pharmaceutical products and incinerated them [169]. To deal with the synthesis of the solvent recovery system, Ahmad et al. [20] proposed a systematic approach for generation of batch processes with integration solvent recovery and recycling and Linninger et al. [21] presented the optimization of structural process flowsheet design decisions while proposing the optimal sequence of a solvent recovery system. Other opportunities of process optimization is energy integration [14], which can reduce the operating costs of a multipurpose

production plant and introduction of process intensification (e.g. integration of reaction-separation) in order to reduce plant footprint, energy and mass required [7].

Process analytical technology (known as PAT) and Quality-by-design (QbD) approaches have an important role in the analysis, development, design and control of pharmaceutical processes by enhancing the process understanding due to fast process knowledge acquisition and establishing the design space in order to ensure that the predefined product quality objectives are satisfied. A systematic method to assist the selection of PAT systems for different process has been proposed by Singh et al. [170] where the critical quality parameters are first identified and the selection is based on economic criteria, reliability criteria and possibilities of integration with a control system. Process control can be established at this point or simultaneously with the design phase using the driving force method proposed by Mansouri et al. [171]. For the evaluation and implementation of different control strategies, the dynamics of the systems need to be known, this can be a challenge for pharmaceutical processes, as the knowledge of the system dynamics are often not know. The final optimal design is then validated through detailed simulation and/or experimentation.

Required data: Optimization targets, variables to be controlled, variables to be monitored.

Information obtained: Process performance criteria, Optimized design, control, and monitoring techniques.

Methods and tools: Plant-wide dynamic models, rigorous model-based simulation tools (ASPEN, SuperPro, ICAS, etc.), ICAS-PAT.

Step D.3. Process operation

Step objective: The pharmaceutical processes are taking place in multipurpose plants where different products are produced at different times. An optimal planning and scheduling should be performed to optimize the use of time, utilities and minimize the operation costs. In addition, process operation should be proposed for processes, which are characterized by their periodic operation. For example, in case of monoclonal antibodies purification using semi-continuous chromatographic columns, an efficient operation strategy needs to be established to maintain continuous operation. Another example, deals with the operation of enzyme-catalysed processes where the process efficiency drops because of the enzyme deactivation, therefore the process operation should be investigated in order to maintained steady state operation.

Required data: Operation objectives.

Information obtained: Operation strategy.

Methods and tools: Plant-wide dynamic models, planning and scheduling methods and tools (SuperPro, Aspen).

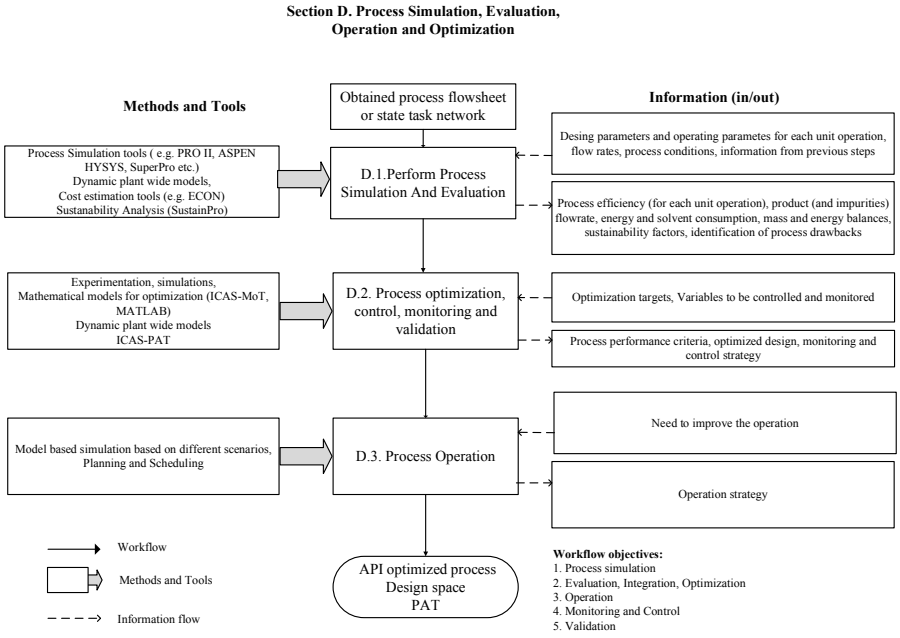


Figure 3.7 Work-flow, methods and tools and data flow corresponding to Section D for the process simulation, evaluation, operation and optimization.

3.4 Conclusions

In this chapter, the overall systematic framework to assist the pharmaceutical process development and investigate opportunities for implementation of continuous manufacturing by enhancing the process understating has been presented. A detailed explanation of the sections and the steps of the systematic framework has been given in terms of objectives, data flow and required methods and tools to achieve the step objective. The developed integrated framework, tackles the pharmaceutical process development problem by providing a data rich environment where the important process variables are identified and their affect in the process can be understood. In this way, the overall process is decomposed in sub-problems: the reaction pathway, reaction analysis, and separation synthesis and process evaluation/optimization. For each sub-problem, a procedure that takes into account all the important aspects of the problem is followed to ensure that a good decision is made based on available data. The framework is suitable for problems related to process synthesis of a completely new process (batch or continuous) or to retrofit an existing process with known or unknown process flowsheet (or state task network). The main objectives of the framework are:

a. The improvement of the reaction pathway (organic or biochemical) by identifying possibilities of improvement and evaluating sustainability metrics.
b. Improvement in the individual reactions in terms of productivity, selectivity, condition selection, and solvent selection.
c. Improvement in reactor design.

d. Evaluation of implementation of continuous manufacturing during the reaction or the wok-up and batch to continuous.
e. Improvement in the synthesis of separation process and determining the type and the sequence of the unit operations.
f. Investigation of process intensification opportunities.
g. Solvent selection for reactions, crystallization, solvent swap, liquid-liquid extraction and distillation.
h. Process evaluation based on mass and energy balances, sustainability metrics, process performance criteria.
i. Process control and monitoring.
j. Process optimization/integration and operation.

4 FRAMEWORK FOR PHARMACEUTICAL PROCESS DEVELOPMENT: SUPPORTING METHODS AND TOOLS

In this chapter, the different methods and tools used within the framework are presented. First, the methods required for the successful implementation of the framework are presented. Second, the computer-aided tools are presented where the methods and tools developed prior to this work or developed by other researchers are briefly explained and the ones developed during this project are explained in detail.

4.1 Methods

4.1.1 Process modelling

For the development of different type of models the systematic modelling methodology proposed by Heitzig et al. [172] is used. The modelling work is divided into four phases and within each phase a sequence of steps is proposed.

- Phase I. Modelling objective and system information

Details for the reasons why the model needs to be developed, variables to be calculated from the model, model accuracy, model application, assumptions, phenomena taking place in the system and available experimental data are defined in Phase I.

- Phase II. Model construction

The mathematical model is constructed, model analysis is performed and solution sequence is defined.

- Phase III. Model identification/discrimination

Parameter estimation, sensitivity analysis and statistical analysis are performed in phase III.

- Phase IV. Model evaluation/validation

Model validation is performed in this step using experimental data that was not used in the parameter estimation.

Once the four phases are completed, the model is ready to be used for simulation and optimization studies. The developed model is then stored in the model library where it can be retrieved and reused.

4.1.2 Multiphase reactive systems modelling

For the model development of multi-phase reactive systems a methodology developed by Anantpinijwtna et al. [173] has been considered. This method consists of modules to describe the physical equilibrium of the compounds between the reaction phases; kinetics and mass transfer based models, and an overall reactor model consisting of the balance equations, the constitutive models (physical equilibrium and kinetic model) and the conditional equations.

4.1.3 Reaction classification

The reaction is then classified according to Roberge et al. [166] classification, which is based on the reaction time: type A (very fast reaction, reaction time < 1 sec, mass transfer controlled), type B (fast reaction, reaction time between 1 sec and 10 min) and type C (slow reaction, reaction time > 10 min).

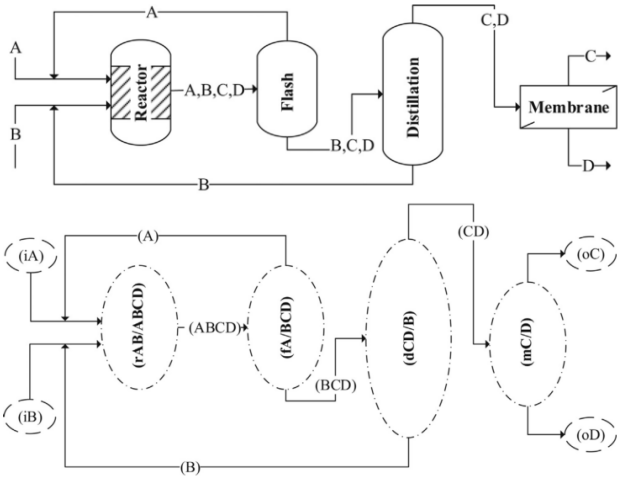
4.1.4 Mass and energy transfer limitations

Mass and heat transfer limitations can be identified according to Hartman et al. [9] roadmap where the reaction mass limitations are evaluated using the Damköhler number (Da, ratio of the reaction rate over the mass transport). If the Da number value is greater than 1, the reaction rate is higher than the mixing rate. Similarly, the heat transfer limitation are evaluated through the β number (produced heat from reaction over rate of heat being removed/added).

4.1.5 Process synthesis

To identify the separation technique and the sequence of the separation tasks, the method proposed by Jaksland et al. [163] and extended by Tula et al. [164] has been considered. The method is based on the thermodynamic insights where the analysis of the compound in terms of thermodynamic properties is essential and based on the relationship between compound properties the separation techniques are identified. Initially, compound are searched in databases such as the CAPEC database [174] and their pure properties are retrieved. In case that the pure compound properties are not available in the databases, then property prediction tools (ICAS-ProPred, part of the ICAS platform [174]) are used in order to estimate the missing properties. Mixture analysis to identify difficult separations such as azeotropic mixtures is performed through databases such as ICAS-AzeoPro (an information based toolbox from ICAS), which identifies the azeotropes and provides a solution for the specific azeotrope. Once the mixture analysis has been performed, the so-called binary ratio matrix, which is the ratio of the each pure component property of all the binary pairs, is created. According to the method developed by Jaksland [163], every operation task can be associated to one or more pure component property. Based on the calculated ratio of the pure properties of the two compound, the process synthesis method, and some additional constrains, the feasible separation tasks for the specific binary pair are identified. Then, the identified separation tasks are combined based on processing rules and the separation objectives. All the combination of the feasible alternative

process flowsheets are generated and represented using as SFILES, which is a text representation of a flowsheet [167]. Figure 4.1 illustrates a process flowsheet, the process groups and the SFILES representation.



SFILES: (iA)(iB)(rAB/pABCD)<1[<(iA)]<2[<(iB)](fA/BCD)1 (dsCD/B)2 (lm(C/D) (oC)(oD)

Figure 4.1 SFILES representation of a process flowsheet [167].

4.1.6 Solvent Selection

For solvent selection problems, the established solvent selection four-step general procedure proposed by Gani et al. [17] has been considered. The solvent selection can be applied to any task that required a solvent to improve the performance of the task. The first step of the procedure is the "Problem identification" where the actual problem and the direction required to solve the problem are identified. In the first step, the need for solvent use is questioned, by investigating whether the operation task can be performed in another way. For example, "is it possible a reaction to be performed in a solvent-free environment?" or "is it possible a solvent-based separation to be performed in other physical separation ways?". In the second step, the criteria that the solvent needs to satisfy must be defined. For example, when solvent is required as a reaction medium it should be a liquid at the operating conditions, therefore, the boiling point at the reaction pressure should be higher than the operating temperature. There are also cases where the solvent has a specific function, for example, it should create a second phase where the product is selectively extracted, therefore, and the reaction product should be more soluble in the extraction solvent than in reaction solvent and the rest of the compound must not be soluble in the extraction solvent. Once the search criteria have been defined, the third step of the procedure is to perform the search. Different approaches might be used to perform the search such as database search, expertise and experience and/or computational (molecular design and/or screening of a predefined list) approaches. The final step of this procedure is the final verification of the selection that can be performed either by using rigorous model-based methods or experimental procedures [17]. The methodology is illustrated in Figure 4.2.

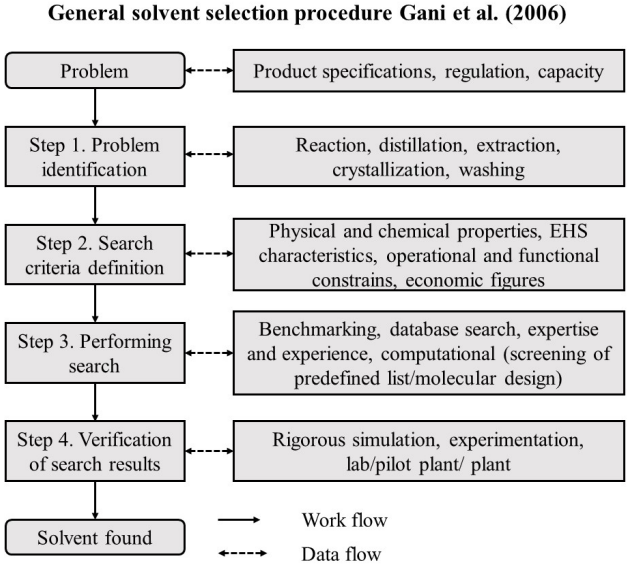


Figure 4.2 General solvent selection methodology proposed by Gani et al. [17].

4.1.6.1 Methodology application

The proposed general methodology for solvent selection has been used in many different problems taking into account the specific needs of the application, such as multi-step organic reaction systems [124], [125], crystallization processes [128], [130] and separation design [175].

4.1.6.2 Solvent swap in pharmaceutical processes

This general procedure (see Figure 4.2) has been applied is the selection of swap solvents for the pharmaceutical processes. It has been extended in this project by adding the specific needs of solvent swap problems in pharmaceutical process.

In pharmaceutical processes, as it has been mentioned, solvents have a multipurpose role since different solvents can be used in different processing steps, such as chemical reaction, separation, and purification of the active pharmaceutical ingredient (API). In these processes, very often, a reaction may take place in solvent-1 (S1) and the next processing step (e.g. reaction, crystallization, extraction, or washing) may require a different solvent-2 (S2), because the process performance is better in S2 than in S1. Therefore, solvent swap (or solvent exchange) is a common and important task in API production line within pharmaceutical industry. In this project, batch distillation is considered as the operation to perform the solvent swap task (see Figure 4.3). In this case, the swap solvent is mixed with the original solvent and the API and enters at the bottom of the batch distillation column. The original solvent is distilled off and collected as the top product while the swap solvent together with the API are collected as the bottom product.

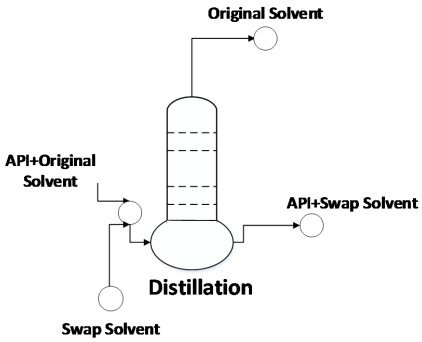


Figure 4.3 General representation of the solvent swap task as a batch distillation operation.

To successfully perform the solvent swap task by batch distillation the solvents (original and swap) must satisfy certain criteria (see Table 4.1), such as boiling point difference between the original solvent and the swap solvent, high average relative volatility between the original and the swap solvent and preferably no azeotrope formation, in addition to the solubility of the solute (API).

Table 4.1 Criteria for good solvent swap.

Criteria	Value	Tool
Boiling point difference	$T_{b,\ Original\ solvent} << T_{b,\ Swap\ solvent}$	Pure compound databases/ Property prediction tools
Average relative volatility	$\alpha_{original\ solvent/swap\ solvent} >> 3$	Pure compound databases/ Property prediction tools
Azeotropes	Preferably no	Databases/ predictive models (i.e. UNIFAC in case of no available experimental data)

The methodology for solvent swap performed by batch distillation is illustrated through a workflow diagram in Figure 4.4. It consists of four main steps, each of which requires specific methods-tools (shown on the left hand side of Figure 4.4) and data-flow (shown on the right hand side of Figure 4.4) for their implementation. The developed methodology has been implemented in the overall integrated framework in Steps B.6 and C.4. It can be applied when it has been identified through the overall framework that the solvent used in a certain processing task cannot be used in the next processing task (see Figure 4.5).

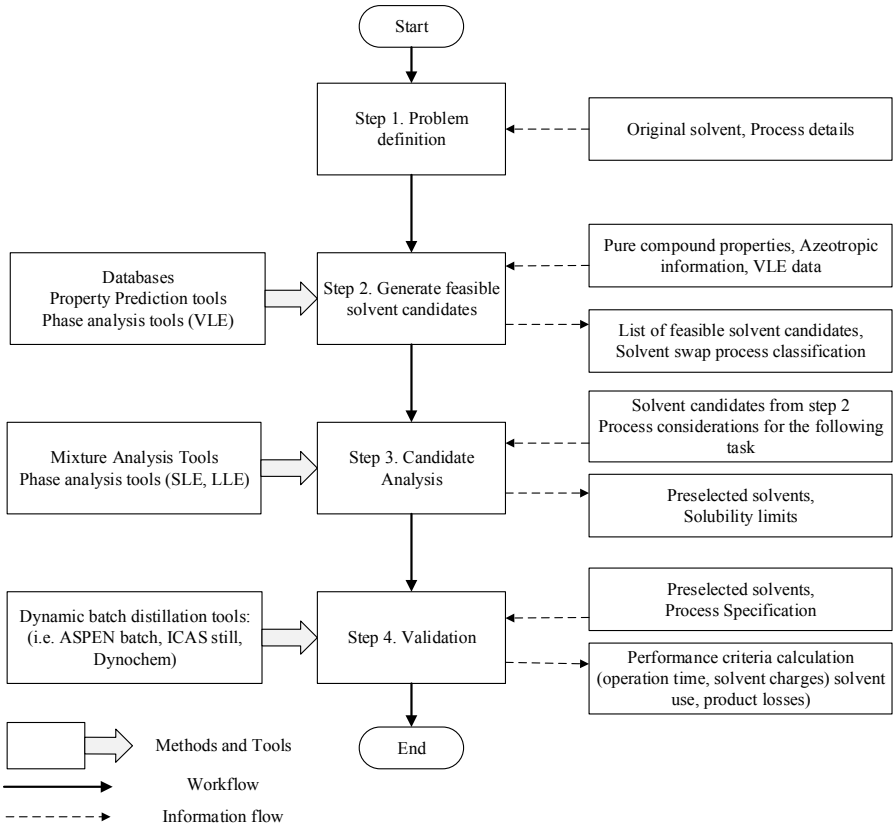


Figure 4.4 Systematic methodology for solvent swap tasks performed by batch distillation.

Step 1. Problem definition

In this step, the swap problem and the objectives of the specific solvent swap task are defined. Details of the original solvent, the process where it is used and the need for replacing it with another are specified (see Figure 4.5). Note however, as shown in Figure 4.5, a number of other tasks also need to be performed after the swap operation. For example, for the synthesis of an API, a reaction task first needs to be performed, followed by different separation tasks. The reaction task requires a solvent (S1, original solvent). However, S1 may not be efficient for the crystallization task following the reactor. Therefore, another solvent (S2, swap solvent) is required. Therefore, the objective of the swap problem is to select a swap solvent that can replace the original solvent through batch distillation and that can perform the separation task efficiently. Alternatively, details for the swap solvent to be used in the separation task can be specified in order to identify a suitable solvent for the reaction task (this is the reverse design solution approach). That is, if a solvent (swap solvent) is the best option for a crystallization task (the downstream processing step) but not very good for the upstream processing step (e.g.

reaction task), which solvent to use for the reaction task so that both processing steps can be performed at high efficiency?

A simple task network of a pharmaceutical process involving a reaction task, a solvent swap task and a downstream processing task that can be performed by reaction, crystallization, liquid-liquid extraction or washing operations, is illustrated in Figure 4.5. In the text below, each of the downstream processing tasks are briefly described.

Solvent swap task

The solvent swap task is employed in order to replace the original solvent with a swap solvent. In this project, only batch distillation is considered for the swap operation, Figure 4.3.

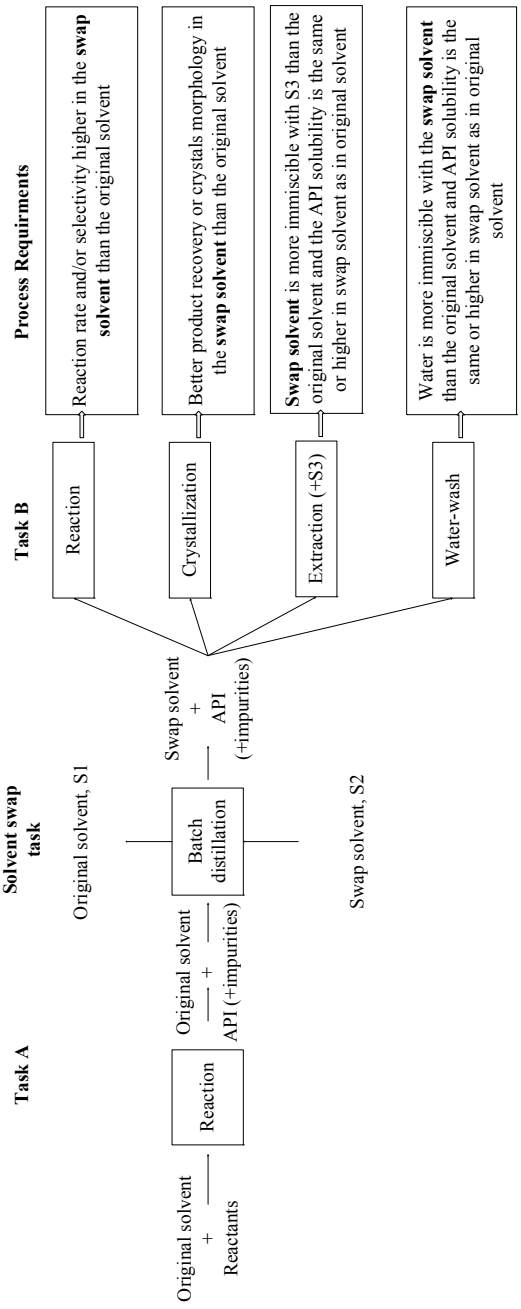


Figure 4.5. Downstream processing options after swap operation.

Step 2. Feasible solvents candidates

The objective of this step is to generate a list of all the feasible swap solvent candidates that can be used to swap the original solvent by batch distillation. The detailed work-flow and data-flow diagram for Step 2 of the methodology is illustrated in Figure 4.3.

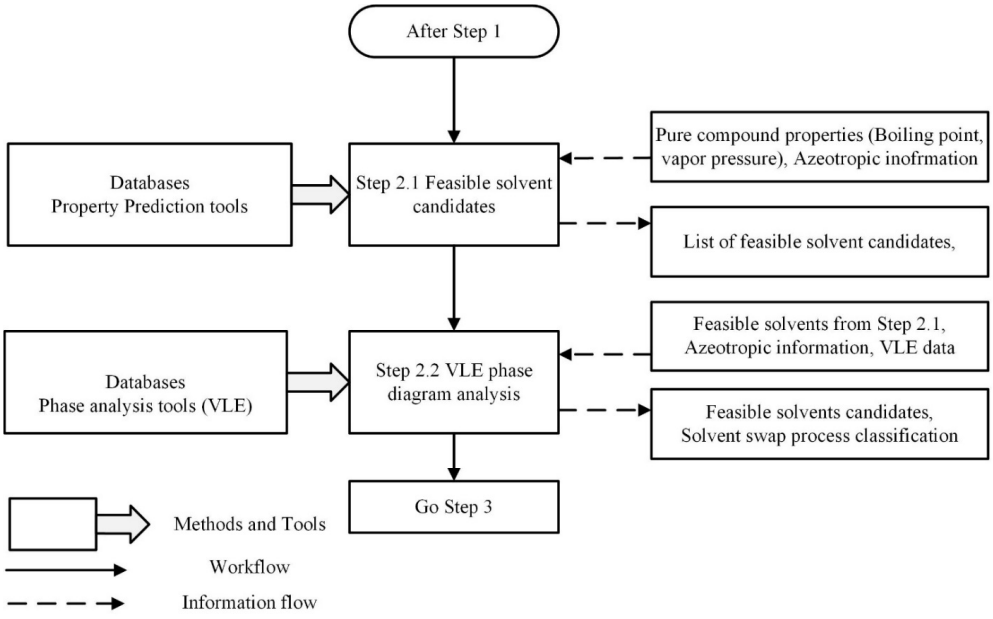


Figure 4.6 Work-flow diagram to identify the list of feasible solvent candidates in Step 2.

Solvent swap task: Batch distillation

Given the original solvent and considering the criteria presented in Table 4.1, the feasible swap solvents for the original solvent are identified through a database search of their target properties and/or by applying computer aided molecular design techniques [17]. Each candidate swap solvent is evaluated in terms of separability from the original solvent through analysis of predicted phase behavior and the separation classified in terms of average relative volatility (α_{aver}): "very easy" when $\alpha_{aver}>>4$; "easy" when $2.5<\alpha_{aver}<4$; "difficult" when $2<\alpha_{aver}<2.5$; "very difficult" when $1.5<\alpha_{aver}<2$; "impossible" when $\alpha_{aver}<1.5$ and "conditional" when an azeotrope is formed. In Figure 4.7, an easy operation and a conditional swap operation are highlighted. The marked areas in Figure 4.7 illustrates the areas of interest for analysis of the VLE (vapor-liquid equilibrium) phase diagrams in batch distillation operations. In the region marked "easy swap", the high temperature pure component point represents the swap solvent and through batch distillation, the original solvent is replaced in the bottom (residue) by the swap solvent. Because of the larger differences between the phase compositions of the involved compound, the batch distillation operation is easier in this region than in any other.

Exceptions to the above criteria do exist, namely, the formation in azeotropes and low average relative volatility where detailed analysis of VLE phase diagrams (see for example, Privat and Jaubert,) are required to investigate the feasibility of the solvent swap task. In the case of minimum boiling point azeotropes, the VLE phase diagrams are used to determine the amount of the fresh swap solvent that must be added to remain in the desired side of the azeotrope, that is, the "conditional swap" region in Figure 4.7. In this case, the bottom (residue) again contains the swap solvent while the top product contains mainly the azeotrope. Note that by operating the batch distillation in the "conditional swap" region, it is also possible to swap a higher boiling point solvent with a lower boiling point swap solvent in the case of minimum boiling azeotropes. Their selection, however, depends on the amount of solvent swap required, operational costs, and the next operational task in the process.

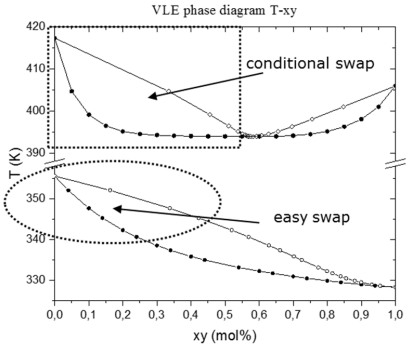


Figure 4.7 Analysis of VLE phase diagrams.

Some azeotropes are known to be pressure sensitive. In the case of pharmaceutical processes, since the compounds involved may be sensitive to high temperatures, the effect of pressure, lower than atmospheric on the azeotrope condition also needs to be considered. In some cases, lowering the pressure, the separation problem becomes easier because of the movement of the azeotrope – see the positive vacuum effect in Figure 4.8. Therefore, a lower pressure operation of the solvent swap task is desirable.

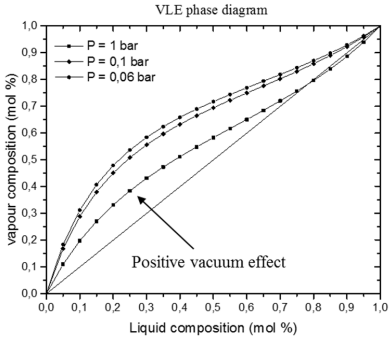


Figure 4.8 The vacuum effect in the binary VLE phase diagram.

Step 3. Candidate analysis

Swap solvents are selected not only for their ability to replace the original solvent by batch distillation but also for their performance in the downstream processing tasks. Depending on the processing task different solvent properties (for example, boiling and melting point temperatures confirm that the swap solvent would remain as a liquid during a specific operation) and phase behaviour (for example, solid solubility is important for crystallization while liquid miscibility is important for extraction) are selected as target properties. The candidate analysis considers all these properties. The properties and the type of phase behaviour important for each downstream processing task are briefly described below.

Solvent properties and phase behaviour

Reaction task

To identify the desired properties of a solvent for the reaction task, the reaction should be analysed in terms of products, reactants, reaction phase, reaction conditions, and solvent role. If, for example, a reactant is in solid state at ambient temperature a solvent that can dissolve this compound is needed, for example, one of the desired properties of the solvent in this case is the solubility parameter of the solvent, which has to be similar to the reactant's solubility parameter. Therefore, the two compounds will be most likely soluble in each other. Also, as these reactions are usually in the liquid phase, the solvent needs to be in the liquid state during the reaction, which means that the boiling point of the solvent needs to be higher than the reaction temperature and the melting point needs to be lower. Another example is, when the solvent needs to have a specific role, such as to create a second phase with the reaction mixture so that the reaction takes place in one phase and the product moves to another phase, which can be evaluated through liquid-liquid equilibrium (LLE) studies. An extensive discussion for solvent selection in organic reactions is found in the literature [124]–[126].

Crystallization task

For solid solubility (or precipitation) calculations, pure compound properties such as melting point (T_m), and the solute enthalpy of fusion (ΔH^{fus}) are required as well as liquid phase activity coefficient (γ_s) of the solute in the solvent calculations. Since experimental data for these properties for APIs may not be available, predictive models (such as UNIFAC[61] and NRTL-SAC [62], [176]) to predict the solid-liquid equilibrium are employed [127]. In addition, in the presence of few experimental data points, the model parameters of the predictive models are regressed or fine-tuned to make the necessary predictions. In this way, the solid solubility calculations using predictive models leads to satisfactory results [127].

Extraction task

For extraction tasks, operations involving solid-liquid equilibria as well as liquid-liquid equilibria are employed to screen the swap solvent candidates. The LLE calculations are required to guarantee the liquid phase split and the SLE calculations are required to determine the operating condition solute recovery with the swap solvent.

Washing task

During the washing step, water is used to remove impurities (such as salt impurities), therefore the swap solvent needs to have a higher capacity to dissolve the API than the original solvent,

and must be immiscible with water. LLE calculation to guarantee the miscibility gap with water, while and SLE calculation verifies the solubility of the solute.

The detailed analysis in Step 3 leads to the preselection of the swap solvents that can be used in the swap process and have the desired process performance for the subsequent processing task.

Step 4. Validation
The objective of this step is to validate the selection of the swap solvent candidates from step 3 through rigorous dynamic batch distillation simulations of the solvent swap operation. Given the initial conditions (composition and temperature), the process specification (operating pressure, boil-up flowrate and the still volume) and having calculated the solubility limits (the minimum volume can be identified for different solvents) the simulation is performed to calculate important process criteria such as operation time, swap solvent charges (in the case of "put and take" swap process), total solvent use, total solvent losses and product loses. The results are used to compare the performance of different solvents in order to identify the best performing solvent with respect to operation criteria and also different solvent swap operation can be compared ("put and take" and "constant volume" operational procedures).

4.2 Knowledge databases

Knowledge database have been created by systematically collecting measured data or calculating data. The data from database can be retrieved and used in different cases.

4.2.1 Reaction database

In this project, a reaction database has been developed with specific focus on reactions taking place in pharmaceutical processes and multiphase reactions within pharmaceutical industry. The reactions in this database have been categorized according to the reaction type, the target product to be produced (when single-step or multistep reactions are considered), the reaction product, and the effect of the solvent use on the reacting system. Reaction conditions (temperature, pressure etc.), reaction compound (reagents, catalysts etc.), reaction data (conversion, selectivity, etc.), scaling information and finally batch or continuous processing. For each reaction entry, a description of the process exists and the references are provided. A more detailed description of the database development and structure follows later. The developed database fulfils criteria that have been defined as necessary for this type of reaction databases [97].

This reaction type database, more specifically aims to:

1. Identify reactions, which are used to produce different types of products (API, Intermediates).
2. Identify reactions to be utilized, for a given compound availability.
3. Investigate the function of different type of solvents in single/multiphase reactive systems.
4. Facilitate the choice of the reaction conditions.
5. Evaluate reaction pathway in terms of yield, cost, sustainability metrics
6. Facilitate the reactor design from available experimental data and kinetic models.

The data required to develop a reaction type database to satisfy the abovementioned objectives has been acquired from numerous published articles and patents. The obtained knowledge from these sources has been structured in a database and stored for easy information retrieval and re-use in different possible applications. The database consists of classes, sub-classes, instances, and objects. A class is a representation for a conceptual grouping of similar terms. Classes are the focus of most ontologies. A class describes concepts in the domain. A class can have subclasses that represent concepts that are more specific than the super class [177].

Knowledge database development

For the development of the reaction type database, the main knowledge categories known as classes are the reaction type, the reaction, phases involved, how the phases are created, solvent use, solvent function, type of solvent, reaction conditions, available data and finally operation mode (listed in Table 2.1). The first knowledge class consists of different reaction types that are commonly found in pharmaceutical processes (e.g. hydrogenation). The set of these reaction types are called the instances of the class. The second class of the knowledge database is the reaction, which is divided in four sub-classes, the reactants, reaction products, and target product and reaction information (see Figure 2.2). The instances of the three first sub-classes of the second class are classified in terms of name of the compound, type of the compound and molecular structure while the forth class summarizes information for the specific reaction. This type of information is crucial to identify the structural changes of the compounds during the reaction. The fourth class of the database consists of instances describing the phases involved in the specific reaction. It is important to note that this class connects the reaction information with the reaction performance class, which will be described later, and it has an important role in the database since in this way, the advantages of using a multiphase or a single-phase system are identified. The next two classes of the database consist of instances describing the solvent function, in case a solvent has been used in the reactive system, for example the solvent function is *"creates a second phase and removes the reaction product"*, and the type and name of the used solvent. The last three classes of the reaction knowledge database consist of instances describing the reaction performance under certain conditions. The reaction conditions class consists of instances, which have to do with the reaction variables such as reaction temperature, amount of reactants, catalyst (type and amount), pH, pressure, and the need to use acid or base. The data class consists of four sub-classes, reaction data, dynamic data, kinetic model, and scale. The instances of the reaction data sub-classes are information related to reaction time (or residence time), conversion, selectivity, reaction yield and overall process yield (usually after isolation and purification). The instances of the dynamic data are sets of experimental data that can be used to fit or to develop a kinetic model. The next sub-class describes the availability of kinetic model that can be used either directly, or after fitting to the experimental data for reaction optimization studies. The last sub-class of the data class provides important information on the scale the reaction has been performed. Finally, the last class of the database is the operation mode, the instances of this class can be different operational modes such as batch reaction or flow reaction.

Database structure

Table 2.1 lists the classes of the databases in the first column, the second column relates the classes with the instances that the classes contain and the third column the list of instances is given for different classes. The structure of the database is visually shown in Figure 2.1.

Table 4.2 Main classes of the reaction type database with the description of the corresponding instances.

Main Classes	Relation with instances	Instance description
Reaction Type, T	**T=**[T1, T2, ..., Ti, …, Tn]	Ti: reaction type in the knowledge base (e.g. acylation etc.)
Reaction, R	**R=**[R1, R2, ..., Ri, …, Rn]	Ri: reaction of the i^{th} reaction type; for each reaction information about the reactants and reaction products are provided as well as information for the target product and process (for example: 1^{st} step for production of an API)
Phases involved, P	**P=**[P1, P2, ..., Pi, …, Pn]	Pi: phases of the i^{th} reaction (e.g. organic-aqueous, organic-gas etc.)
How phases are created, C	**C=**[C1, C2, ..., Ci, …, Cn]	Ci: (e.g. solvent etc.)
Solvent function, F	**F=**[F1, F2, ..., Fi, …, Fn]	Fi: (e.g. phase creation, carrier etc.)
Solvent type, ST	**ST=**[ST1, ST2, ..., STi, …, STn]	STi: (e.g. ether, alcohol etc.)
Solvent, S	**S=**[S1, S2, ..., Si, …, Sn]	Si: Solvents in i^{th} reaction
Reaction condition, RC	**RC=**[RC1, RC2, ..., RCi, …, RCn]	RCi (e.g. Temperature, composition, cat, pH etc.)
Data, D	**D=**[D1, D2, ..., Di, …, Dn]	Di (reaction data: conversion, selectivity, reaction time, and dynamic data: concentration vs. time, scale information and kinetic models etc.)
Operation Mode, OP	**OP=**[OP1, OP2, ..., OPi, …, OPn]	OPi: batch, continuous, fed batch

In Figure 4.6 the graphical representation of the reaction type database is illustrated.

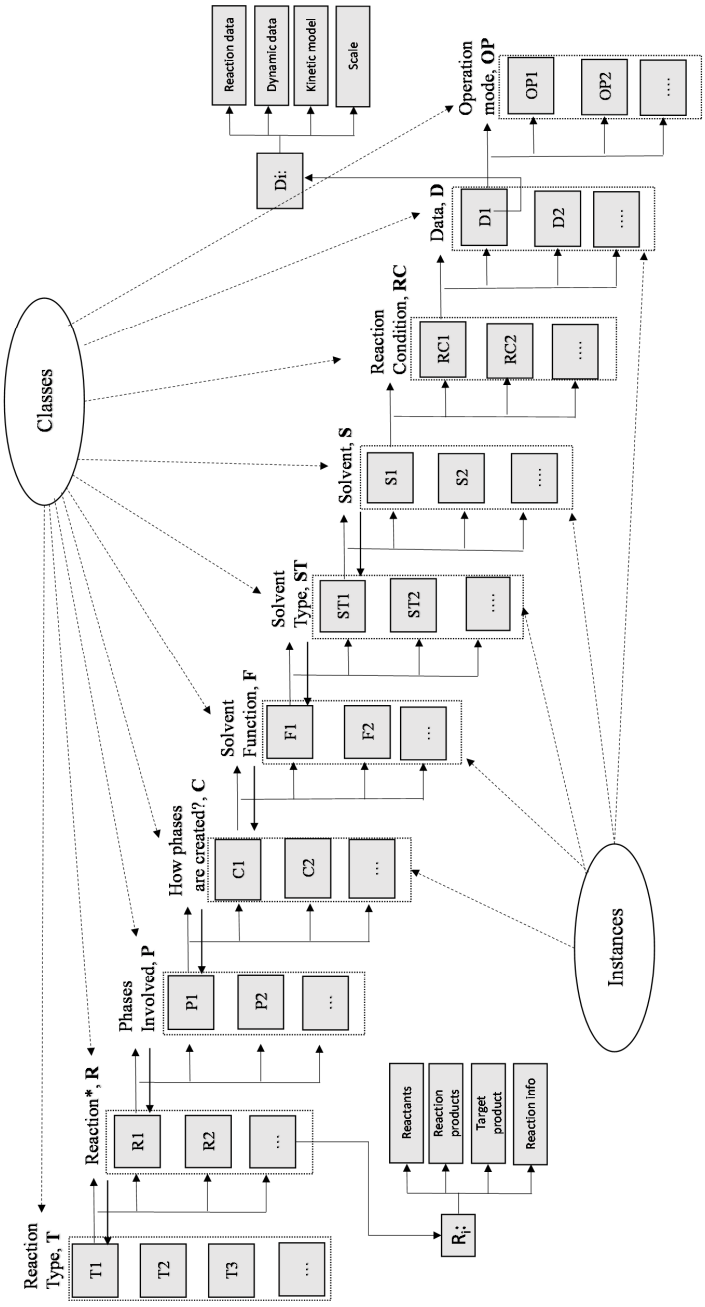


Figure 4.9 Graphical representation of the structure of the reaction type database.

In Figure 4.7 the subclasses and the values of each instance in the "Reaction" class are described. For example each reaction has **reactants**, **reaction products** and it can be used to eventually produce a **target product** (in case of multi-step reactions), each of the sub-classes take values such as the name of the **compound (N),** the **type of the compound** (T, for example, alcohol) and the **structure** of the compound. The reaction info subclasses takes text values that can be used to give useful insights for the reaction.

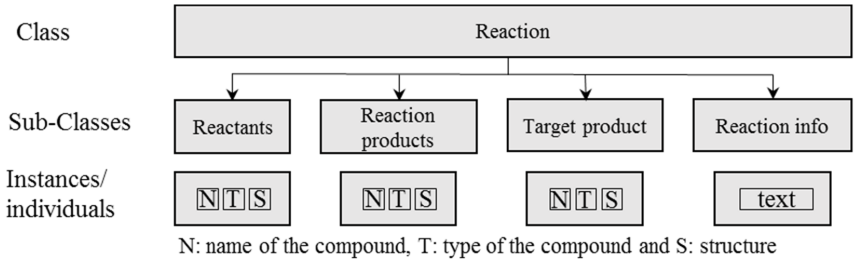


Figure 4.10 Representation of the sub-classes of the "Reaction, R" class, together with the corresponding instances.

4.2.2 Unit operation database

A database which provides information for different unit operations (batch, continuous or batch to continuous) has been developed. This database is based on published examples from literature where the reaction system converted from batch to continuous or the unit operation is operated in continuous mode. It provides an information-based selection procedure which takes into consideration the main design parameters (such as residence/reaction time, heat transfer and mass transfer limitation) and phases presence in the reaction. The selection has to be further evaluated either by performing experiments or developing detailed reaction models. Table 4.3 lists the criteria to choose between continuous reactors.

Table 4.3 Chossing between continuous reactor [178].

Reactor Mode	CSTRs	PFR	Microreactor
Handling of solids	++	-	--
Gas evolution	++	-	--
Slow reaction kinetics	++	-	--
High conversion per volume	-	++	++
Narrow residence time distribution	-	++	++
Initial heat sink	+	-	-
Low operational complexity	-	++	--
Low level of equipment intensity	+	++	--
Enhanced heat transfer	-	+	++
Enhanced mass transfer	-	+	++
Low cost	+	+	--

Unit operation database structure

Figure 4.11 illustrates the graphical structure of the unit operation database.

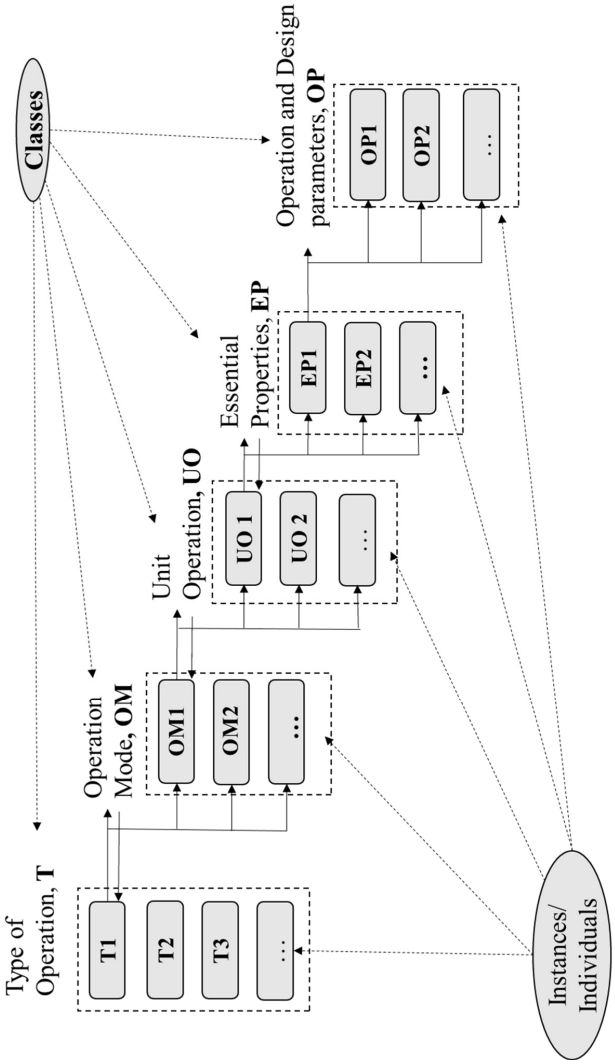


Figure 4.11 Graphical representation of the unit operation database.

Table 4.4 lists the classes of the databases in the first column, the second column relates the classes with the instances that the classes contain and the third column the list of instances is given for different classes.

Table 4.4 Main classes of the unit operation database and description of the corresponding instances.

Main Classes	Relation with instances	Instance description
Type of operation, T	**T=**[T1, T2, …, Ti, …, Tn]	Ti: operation type in the process(e.g. synthesis, purification)
Operation mode, OM	**OM=**[OM1, OM2, …, Omi, …, Omn]	Omi: operation mode of the unit operation Ti (e.g. batch purification)
Unit operation, UO	**UO=**[UO1, UO2, …, Uoi, …, Uon]	Uoi: unit operation of the i^{th} operation type and operation mode (e.g. continuous synthesis, CSTR)
Essential properties, EP	**EP=**[EP1, EP2, …, Epi, …, Epn]	Epi: important primary (relative volatility) and mixture properties (LLE)
Operation and design parameters, OP	**OP=**[OP1, OP2, …, Opi, …, Opn]	Opi: operation parametes (e.g. temperature, pressure), design variables (e.g. residence time)

4.2.3 Solvent Swap database

This database consists of solvents that are commonly used in pharmaceutical processes and provides information on the feasibility of the solvent swap task. The objective of this database is to provide the data required for the calculations in Steps 2-4 of the solvent swap methodology. The solvents that are included in the database are listed in Table 4.5 with values for a selected set of pure compound properties, such as boiling point temperature (T_b), melting pointing temperature (T_m) and solubility parameter (SolPar). The solvents listed in Table 4.5 can also be considered a special set because another from the list can swap them.

Table 4.5 Solvents commonly used in pharmaceutical processes. Bold numbers: predicted using ICAS-ProPred.

Solvent	Formula	CAS	MW (gr/mol)	T_b (°C)	T_m (°C)	SolPar ($MPa^{½}$)
Dichloromethane (DCM)	CH_2Cl_2	75-09-2	84.93	39.8	-95.1	20.4
Methyl tetr-butyl ether (MTBE)	$C_5H_{12}O$	1634-04-4	88.15	55.2	-108.6	15.1
Acetone	C_3H_6O	67-64-1	58.08	56.0	-94.8	19.7
i-hexane (or 2-methly pentane)	C_6H_{14}	107-83-5	86.18	60.2	-153.7	14.4
Methanol (MeOH)	CH_4O	67-56-1	32.04	64.8	-97.6	29.6
Tetrahydrofuran (THF)	$C_4H_8O_2$	109-99-9	72.11	65.0	-108.3	19.0
Ethyl acetate (EtAc)	$C_4H_8O_2$	141-78-6	88.11	77.1	-83.6	18.3
2-methyltetrahydrofuran (MeTHF)	$C_5H_{10}O_2$	96-47-9	86.30	78.0	**-80.7**	**18.3**
Methylethyl ketone (MEK)	$C_4H_8O_2$	78-93-3	72.11	79.5	-86.6	18.9
Acetonitrile (MeCN)	C_2H_3N	75-05-8	41.05	81.6	-43.8	24.1

2-propanol (IPA)	C_3H_8O	67-63-0	60.10	82.3	-89.5	23.4
Isopropyl acetate (IPAc)	$C_5H_{10}O_2$	108-21-4	102.13	88.6	-73.4	17.2
Water	H_2O	7732-18-5	18.01	100.0	0.0	47.8
Toluene	C_7H_8	108-88-3	92.14	110.6	-94.9	18.3
Methyl-isobutyl-ketone (MIBK)	$C_6H_{12}O$	108-10-1	100.16	116.5	-84.0	17.4
Acetic acid	$C_2H_4O_2$	64-19-7	60.05	117.9	16.6	19.0
N,N-Dimethylformamide (DMF)	C_2H_7NO	68-12-2	73.10	152.0	-60.4	23.9
Anisole (or methoxybenzene)	C_7H_8O	100-66-3	108.14	153.7	-37.5	20.1
N-Methyl pyrrolidone (NMP)	C_5H_9NO	872-50-4	99.13	202.0	-24.0	23.2
Ethanol (EtOH)	C2H6O	64-17-5	46.07	78.2	-114.1	26.1
1-Butanol (n-BuOH)	$C_4H_{10}O$	71-36-3	74.12	117.7	-89.8	23.3
2-methyl-1-propanol (iso-BuOH)	$C_4H_{10}O$	78-83-1	74.12	107.8	-108.0	22.9

The feasibility of the swap operation for each pair of solvents in this database has been check through rigorous dynamic simulations of the corresponding batch distillation operations. Taking also into account the criteria for good solvent swap (Table 4.1), the azeotropic information collected for each pair, the VLE phase diagrams and the vacuum effect on VLE, a selection guide for swap solvents (and the reverse problem) has been developed. Figure 4.12 and Figure 4.14 illustrate these selection guides while Table 4.6 lists some of the conditional swap information.

Figure 4.12, Figure 4.13 and Figure 4.14 show for each pair of solvents, the feasibility of the swap operation. Based on the simulated data, the swap operation is classified in terms of very easy (I), easy (II), difficult (III), very difficult (IV), impossible (X) and conditional (CXX). In Figure 4.12, the original solvents are placed on the diagonal axis and the swap solvents are placed on the vertical axis. Therefore, for any given original solvent, the feasibility of its replacement by a swap solvent can be determined by simply checking the entire swap solvents listed in the corresponding column, while for a swap solvent, the feasibility of all the original solvents it could replace can be found by checking the original solvents listed in the corresponding row. Figure 4.13 shows similar information but with the swap solvents in the diagonal axis and the original solvents in the vertical axis.

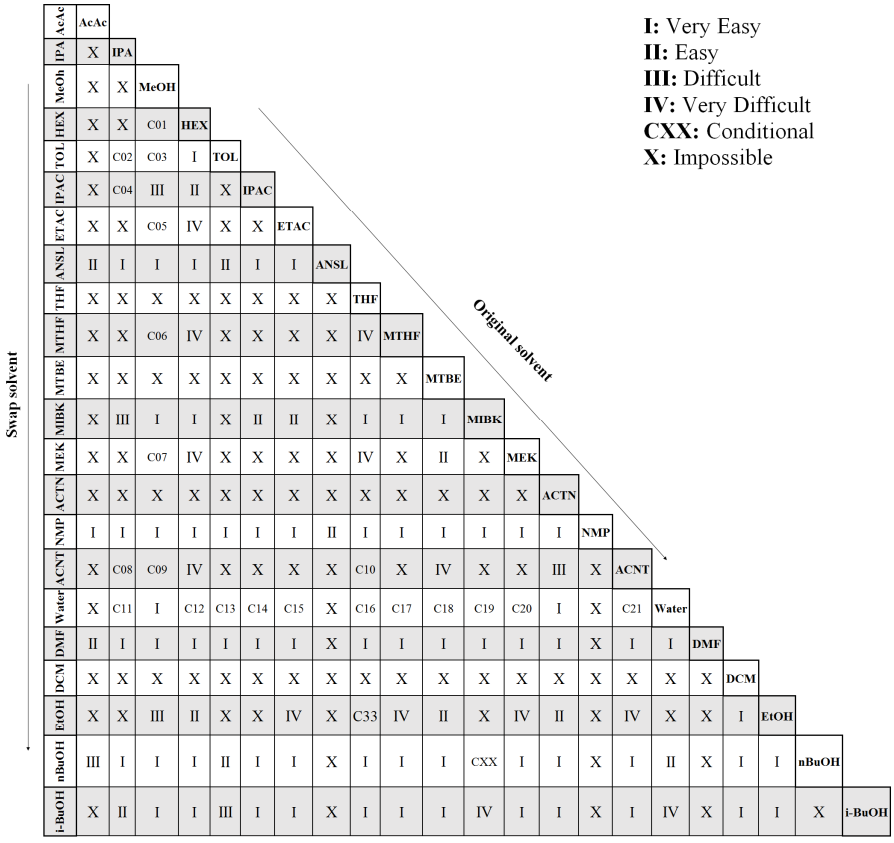


Figure 4.12 Feasibility of swap operation for different solvent pairs(swap solvent versus original solvent). Classification of swap operation in terms of very easy (I), easy (II), difficult (III), very difficult (IV), impossible (V) and conditional (CXX).

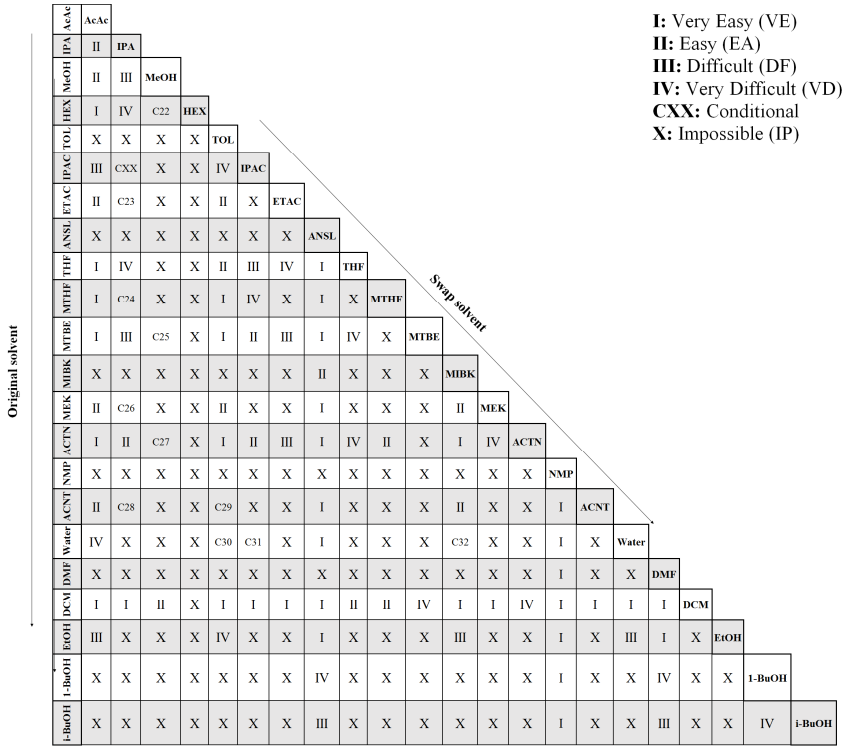


Figure 4.13 Feasibility of swap operation for different solvent pairs (original solvent versus swap solvent). Classification of swap operation in terms of very easy (I), easy (II), difficult (III), very difficult (IV), impossible (V) and conditional (CXX).

Figure 4.14 shows the effect of vacuum application on the solvent swap task. This guide is used to identify for conditional swap operation, whether or not vacuum is beneficial.

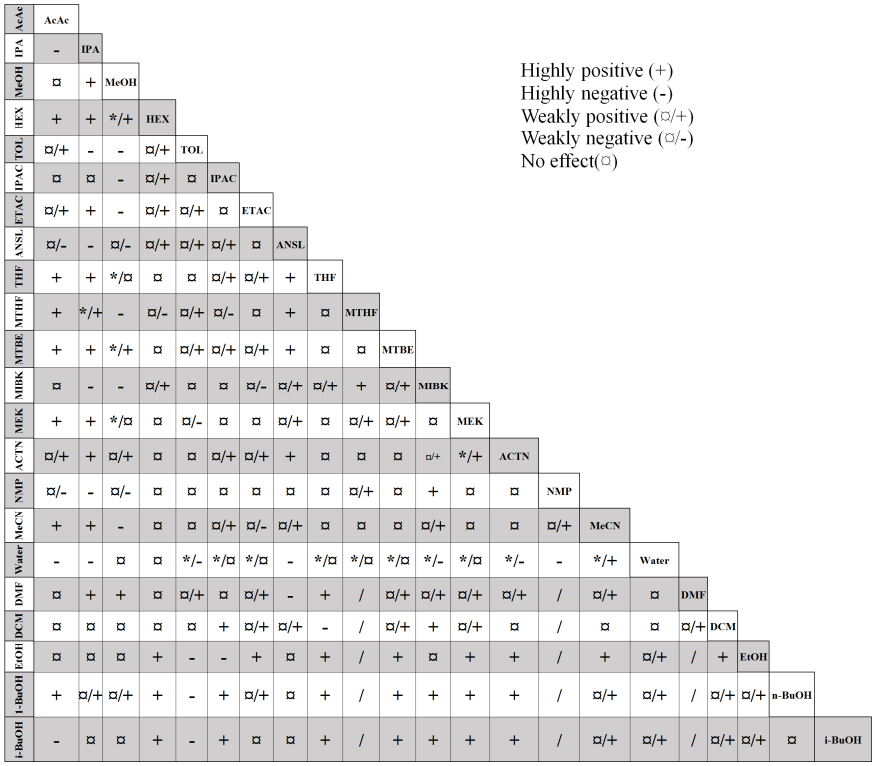


Figure 4.14 The effect of the vacuum on the swap operation (VLE phase diagram). Positive effect means the vacuum makes the separation easier. Negative effect means that the vacuum makes the separation more difficult. No effect means that vacuum make the separation neither more difficult nor easier.

The solvent pairs that form a minimum boiling azeotrope have been classified as conditional in terms of the solvent swap task that will need to be performed if they are involved. Therefore, when such a pair is encountered, the amount of the swap solvent to be charged for batch distillation should be such that the solvent-swap solvent mixture will lie in the conditional swap region (see Figure 4.7). This would then guarantee a batch residue containing the swap solvent plus the reaction product while the original solvent plus low boiling impurities will be removed as the distillate product. For the conditional swap pairs found and stored in the database (Figure 4.12 and Figure 4.14), the corresponding azeotrope composition of the solvent is listed in Table 4.6 in terms of mass and mole percent. In addition, through simulations of batch distillation involving each pair, the swap operation is classified.

Table 4.6 List of the conditional solvent pairs together with their azeotropic composition and swap operation classification. Solvent pairs classified as "Conditional" swap operation, together with the maximum mixture composition in terms of original solvent (*) and classification are listed.

	Conditional solvent pair		Azeotrope Composition (original solvent)		
	Original	**Swap**	**mol%**	**mass%**	**Classification**
C01	Methanol	i-hexane	65	85	EA
C02	IPA	Toluene	25	35	VE
C03	Methanol	Toluene	25	45	VE
C04	IPA	IPAC	45	60	VD
C05	methanol	ETAC	40	65	VD
C06	methanol	MTHF	35	20	DF
C07	methanol	MEK	35	55	DF
C08	IPA	MeCN	60	5	DF
C09	Methanol	MeCN	35	40	EA
C10	THF	MeCN	25	20	VE
C11	IPA	water	45	20	VE
C12	i-hexane	water	20	10	VE
C13	Toluene	water	60	25	DF
C14	IPAC	water	50	20	VE
C15	ETAC	water	40	20	VE
C16	THF	water	30	10	VE
C17	MTHF	water	40	15	EA
C18	MTBE	water	20	10	VE
C19	MIBK	water	70	35	EA
C20	MEK	water	40	15	VE
C21	ACNT	water	40	25	VE
C22	i-hexane	Methanol	50	30	VE
C23	ETAC	IPA	40	35	VD
C24	MTHF	IPA	40	35	VD
C25	MTBE	Methanol	45	25	DF
C26	MEK	IPA	45	40	VD
C27	acetone	Methanol	40	25	VD
C28	MeCN	IPA	55	65	DF
C29	MeCN	Toluene	25	45	VE
C30	water	Toluene	50	85	EA
C31	water	IPAC	65	95	DF
C32	water	MIBK	40	80	EA
C33	THF	Ethanol	9	6	EA

Note: EA= Easy; DF= Difficult; VD= Very difficult; VE=Very easy

All the necessary calculations for Step 2 of the methodology have been performed during the creation of the swap solvent database (represented by Figure 4.10 -Figure 4.14 and Table 4.6). Therefore, unless a solvent not listed in the database is used, no calculations are required for step 2. Figure 4.12-Figure 4.14 and Table 4.6 are used as a guide for the quick identification of the swap solvents, when the original solvent is known or vice versa.

4.2.4 Pure compound database

The CAPEC database contains information of pure compound properties and it is used to extract the pure compound properties of the compound. In addition, VLE experimental data, interaction

parameters for VLE analysis (e.g. UNIFAC parameters), and miscibility calculations/ information are available [174].

4.2.5 Monitoring and control database

The PAT knowledge database has been developed prior to this project by Singh et al. (2010) and it aims to support the selection of suitable process monitoring and analysis tools for a specific application or process and to support the search for the range of potential applications of a specific monitoring tool [177]. The ICAS-PAT database includes information for monitoring and control for fermentation processes (tasks: fermenter, mixing task and steriliser), tablet manufacturing process (tasks mixing, milling, granulation, tablet storage, tablet press and tablet coater) and for cheese manufacturing processes (tasks: milk storage tank, pasteurizer and cooling system). The monitoring and control database also needs to be expanded including the advances of PAT and control technologies for different types of equipment involved in pharmaceutical processes, for example, crystallization (different types of batch and continuous crystallizers) and reactors (including the new technologies, e.g. microwaves).

4.2.6 Model libraries

Model libraries are essential for the application of the framework as generic developed models can be stored, retrieved, and used for the analysis and simulation of the defined system.

4.2.6.1 Process models

Generic process models are needed for the simulation and analysis of different unit operations. For most of the common unit operations, process models have already been developed and implemented in templates, which can be easily retrieved and reused in many different applications. In this field, a development for the pharmaceutical processes is required because of the introduction of new technologies (e.g. micro-fluid). Therefore, new models based on first principles have to be developed in order to simulate new technologies.

4.2.6.2 Property prediction models

Pure compound properties for APIs and solvents that are not available in the CAPEC database are predicted by the methods available in ICAS-ProPred. The only information needed is the molecular structural information of the compounds.

4.2.6.3 Kinetic models

A library of kinetic models is essential for the kinetic modelling of the reactions because the use of the library can be of great assistance when a new kinetic model needs to be developed.

4.3 Computational Tools

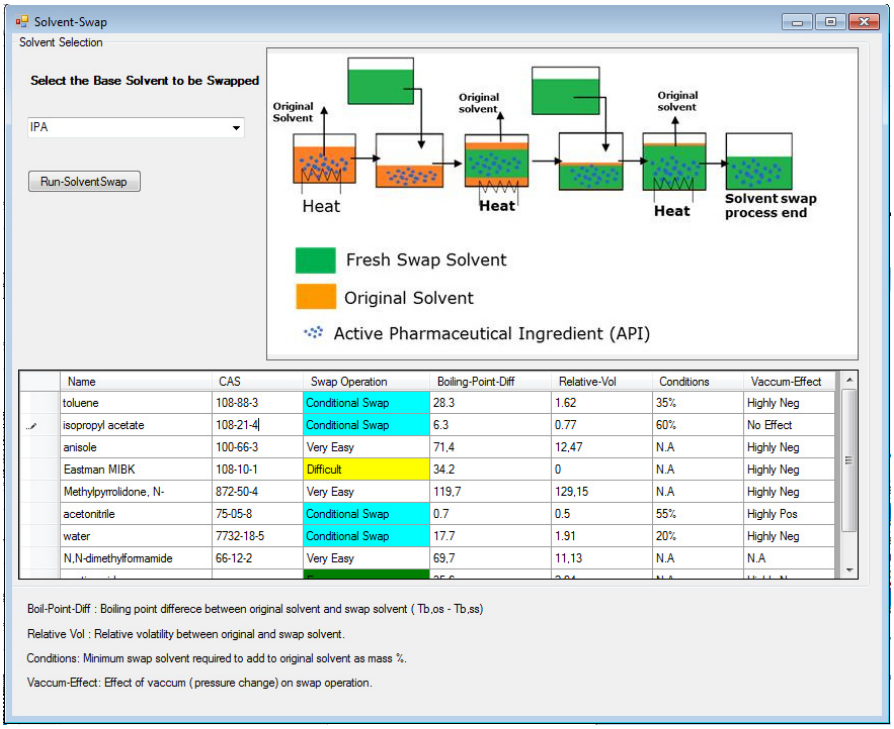
The computational tools are necessary for the generation of required data, which is needed, for the application of the presented framework and the methodologies. A general description of the computational tools is provided, shifting the emphasis on the developed tools during this project. The computational tools are classified as, mathematical solvers, solvent design/analysis and selection tools, process synthesis, simulation and evaluation tools.

4.3.1 Mathematical solvers

To solve the developed models, mathematical solvers such as ICAS-MoT and MATLAB ® can be used.

4.3.2 Solvent design, analysis and selection

Computer aided tools have been developed by Gani et al. for solvent selection, design and analysis and implemented in ICAS platform. ICAS-ProCAMD is a tool developed for solvent selection and design, this tool is based on predictive thermodynamic models based on group-contribution models. In combination with atom connectivity rules it generates molecules that have predefined desired pure component and mixture properties. The search can be limited to compounds that are known in the database but it is also able to design new molecules [179]. Another tool that has been developed by the same group, ICAS-SolventPro, which is used for the solvent analysis. ICAS-SolventPro assists in the selection and analysis for solvents for different unit operation where a solvent is required, solvent selection for organic reactions, solvent screening and mixture design and a new option is swap solvent selection [180]. Solubility calculation and solid-liquid equilibria can be performed using predictive models such as UNIFAC [61], PC-SAFT [63], and NRTL-SAC [62], when experimental data is available, it can be used to estimate the model parameters so the prediction becomes more reliable. For the swap solvent selection, the tool is able to identify all the solvents that are suitable for the swap process (when batch distillation is considered as the swap task), the data for solvent swap behind the tool is based on the developed database for swap solvent selected which has been explained in Section 4.2.1.3. A screenshot of the tool for swap solvent selection is illustrated in Figure 4.15.



Name	CAS	Swap Operation	Boiling-Point-Diff	Relative-Vol	Conditions	Vaccum-Effect
toluene	108-88-3	Conditional Swap	28.3	1.62	35%	Highly Neg
isopropyl acetate	108-21-4	Conditional Swap	6.3	0.77	60%	No Effect
anisole	100-66-3	Very Easy	71,4	12,47	N.A	Highly Neg
Eastman MIBK	108-10-1	Difficult	34.2	0	N.A	Highly Neg
Methylpyrrolidone, N-	872-50-4	Very Easy	119,7	129,15	N.A	Highly Neg
acetonitrile	75-05-8	Conditional Swap	0.7	0.5	55%	Highly Pos
water	7732-18-5	Conditional Swap	17.7	1.91	20%	Highly Neg
N,N-dimethylformamide	66-12-2	Very Easy	69,7	11,13	N.A	N.A

Figure 4.15 Screen-shot from the main page of ICAS-SolventPro. The solvent swap computer aided tool is integrated with the ICAS-SolventPro which is part of ICAS platform [174].

4.3.3 Process synthesis

Pro-CAFD is a computer aided-tools that has been developed by Tula et al. and it is based on the process synthesis methodology published in [164].

4.3.4 Process simulation tools

The role of process simulation in pharmaceutical process is to validate the decisions taken during the process development and to perform the energy and mass balances calculations for the developed processes. The simulation results can be used to:

a. Calculate process performance criteria such as product quality, production time, resources required (e.g. solvent), energy required and generated waste.
b. Perform process analysis in terms of economics and sustainability by using process evaluation tools (discussed in section 4.3.5).
c. Validate new design proposed based on the process evaluation analysis.
d. Perform process optimization.
e. Planning and scheduling.

Tools such as AspenTech/Aspen-batch, Scale-up Systems/Dynochem, Intelligent Inc./SuperPro and ICAS platform [174] can be used.

4.3.5 Process evaluation

Process evaluation tools such as cost analysis, LCA, sustainability analysis (ICAS SustainPro), "green" metrics (see Table 4.7) are important for the analysis of the developed process. The process analysis is used to identify possible process hotspots that can be translated to optimization targets. The reviewed by Constable et al. [133] "green" metrics are listed in Table 4.7, where for each metric, an explanation and the equation to quantify a specific metric are given.

Table 4.7 Metrics for "green" chemistry as they have been proposed to literature. Reviewed by Constable et al. [133].

Metric	Explanation	Equation
Effective Mass yield (EM)	the percentage of the mass of product over the overall mass of non-begin compounds used during the synthesis	$EM(\%) = \frac{Mass\ of\ products\ (kg)}{Mass\ of\ non-benign\ reagents\ (kg)} x100\%$
E-factor	The mass of total waste produced for a given amount of produced product	$E-factor = \frac{Total\ waste\ (kg)}{kg\ product}$
Atom Economy	How much of the reactants remain in the product	$Atom\ Economy(\%) = \frac{MW\ P}{\sum(MW\ A,B,D,F,G,I)} x100$ Where A, B, D, F, G, I: reactants; P: product
Mass Intensity (MI)	Total mass used to produce the product	$MI = \frac{Total\ mass\ used\ in\ a\ process\ or\ process\ step\ (kg)}{Mass\ of\ product\ (kg)}$
Carbon efficiency	Percentage of carbon of the reactants that remain in the final product	$Carbon\ efficiency\ (\%) = \frac{amount\ of\ carbon\ in\ product}{Total\ carbon\ present\ in\ reactants} x100$
Reaction mass efficiency (RME)	Mass of reactants remaining in the product	$RME\ (\%) = \frac{mass\ of\ product(kg)}{mass\ of\ reactants\ (kg)} x10$

5 CASE STUDIES

In this chapter, four case studies are presented, highlighting in each one of them the applicability of the framework. The first case study deals with process analysis and development of the process for the production of ibuprofen. The second case study deals with the swap solvent selection problems where the developed solvent swap methodology is applied in four different examples. The third case study deals with process intensification of a multiphase reactive system. The final case study deals with process operation problem for productivity improvement of a reactor plant.

5.1 Case study 1: Ibuprofen synthesis

Ibuprofen (2-(4'-isobutylphenyl) propionic acid) has been selected as the target compound for the application of the integrated framewok. Ibuprofen is a well-known nonsteroidal anti-inflammatory drug (NSAID) used for relieving pain, alleviating fever, and reducing inflammation. Ibuprofen was derived from propanoic acid by the research of Boots Company during the 1960s and patented in 1961. The original Boots synthesis of ibuprofen consisted of six steps, started with the Friedel-Crafts acetylation of isobutylbenzene. Reaction with ethyl chloroacetate (Darzens reaction) gave the α,β-epoxy ester, which was hydrolysed and decarboxylated to the aldehyde. Reaction with hydroxylamine gave the oxime, which was converted to the nitrile, then hydrolysed to the desired acid [181].

5.1.1 Problem definition

The objective of this case study is to:

- Investigate the reaction pathways to produce ibuprofen.
- Perform reaction analysis.
- Generate the state-task network (or the flowsheet) to produce high purity ibuprofen crystals.
- Generate process alternatives.
- Perform process analysis/simulation and evaluation.
- Target production: 75 kg per batch.

5.1.2 Section A. Reaction pathway identification

Step A.1. Select API or intermediate: **Ibuprofen**

Step A.2. Reaction pathway identification: Using the reaction type database and searching for "Ibuprofen" as the target product (the search and the results are illustrated in Figure 7.1 in chapter 7, Appendix A) three reaction pathways have been found. The currently used process which has been published by Elango et al. [182] and it consists of three reaction steps, a Friedel craft acylation, a hydrogenation and finally, a carbonylation step. The individual reaction steps of the selected pathway have been the focus of reaction optimization studies by many research groups. The other two reaction pathways have been recently discovered independently by McQuades's group [147] and Jamison's group [148], both pathways consist of a Friedel crafts acylation, an aryl migration step and a saponification step. The BHC pathway [182] is illustrated in Figure 5.1, the details for the other two reaction pathways are illustrated in Figure 7.2 in Appendix A.

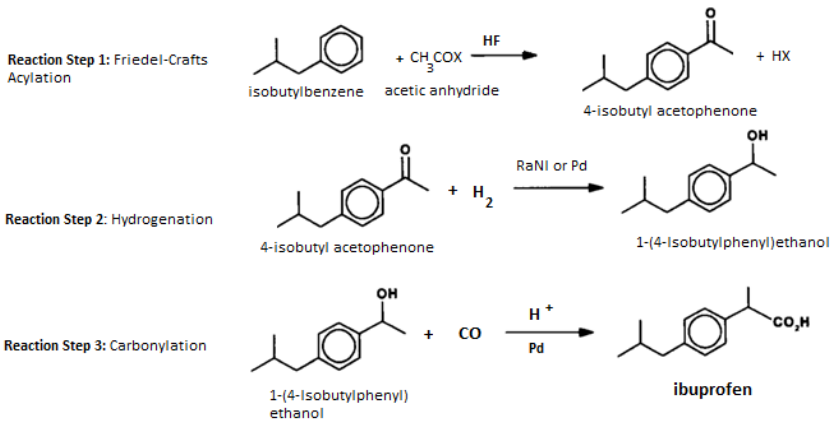


Figure 5.1 BHC reaction pathway, obtained from Elango et al. [182].

A simple evaluation based on "green" metrics (Table 4.7) has been performed and illustrated in Figure 5.2. For the analysis the BHC pathway without and with recycle of HF and IBB, the pathways proposed by Bogdan et al. [147], and by Snead et al. [148] have been considered. The effective mass yield (EM), which is a ratio of the produced product (in mass, kg) over the total amount of non-benign reactant, has been first evaluated. As it is illustrated in Figure 5.2, the step 1 of the BHC synthesis requires larger amounts of non-benign reactants compared to pathway 2 and 3, whereas the reaction step 2 and 3 require much less non-benign reactants. Another metric that has been evaluated is the mass intensity (MI), which shows the total required mass for the reaction per kg of product. In Figure 5.2, it can be seen that the first reaction steps of the pathway 2 and 3 require less amount of reactants than the amount required for BHC without considering the recycle. However, when recycle is considered, the MI metric has lower values for BHC pathway than the other two pathways where recycle is not possible. In addition, the pathway proposed by Snead et al. [148] requires much less amount of reactants

than what is required in pathway 3. The E-factor metric shows the generated waste per kg of product. The first step of BHC pathway has been found to be the main contributor in the E-factor metric, even if the step 1 produces a small amount of waste during the reaction, the large value of E-factor comes because large stoichiometric amounts of solvent and reactant are needed. When the solvent and the reactant are recycled back in the reactor, the E-factor reduces dramatically while the small value of e-factor is because the small amount of non-recovered solvent and reactant (~1%). The other two pathways have relatively higher values of E-factor, which means that larger amounts of waste are generate through the synthesis. The generated waste for the proposed pathway by Snead et al. has been found slightly less compared to the reaction pathway proposed by Bogdan et al.

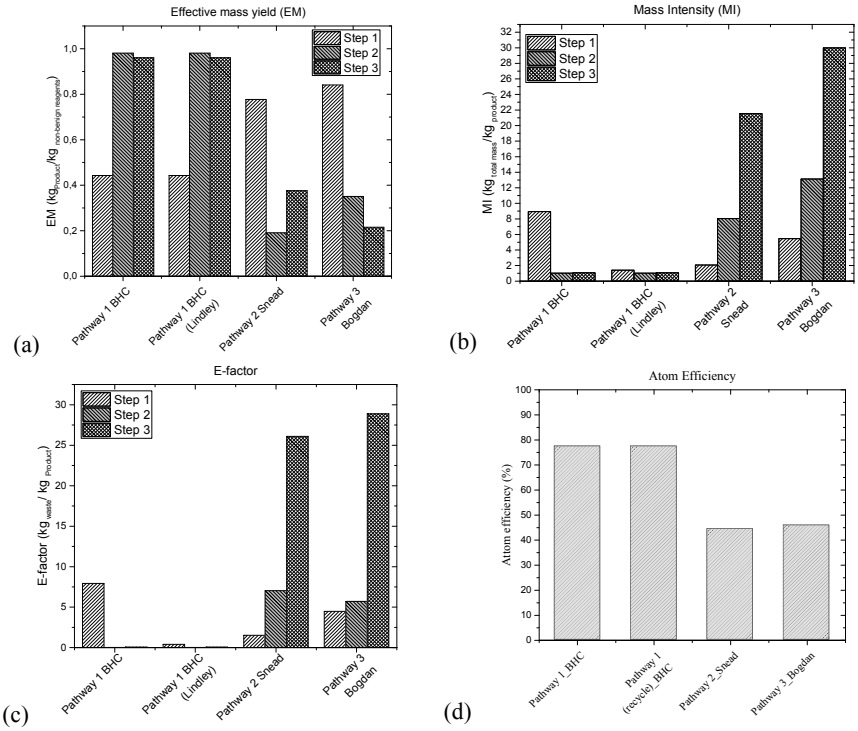


Figure 5.2 Green metrics evaluation for the reaction pathways found in reactiontype database.

Finally, the atom efficiency has been evaluated for the all the reaction pathways and is illustrated in Figure 5.2 (d). It can be seen that the atom efficiency for the BHC reaction pathway is higher than the other two pathway as most of the atoms in the reactants remain in the final product. Whereas, the atom efficiency is much lower for the two recently developed flow pathways, which means that these pathways generate more waste than the BHC pathway.

5.1.3 Section B. Reaction analysis

Step B.1 Data collection.

Reaction Step 1. Friedel-Craft acylation

The ibuprofen synthesis starts with an acylation through Friedel-Craft reaction, where isobutylbenzene (IBB) reacts with an acetylating agent (acetic anhydride) to produce 4-isobutylacetophenone (4-IBAP). The reaction phase consist of two phases a hydrogen fluoride rich phase which consists of acetylating agent, the reaction product and small amount IBB that is slightly soluble in HF, and the IBB rich phase. The catalyst for this reaction is hydrogen fluoride as it acts as a strong Lewis acid, which is required for the Friedel-Crafts acetylation. The reaction data has been retrieved from the reaction database and it is given in Table 5.1.

Table 5.1. Prelimenary data collected for Friedel-Craft acylation step.

Reaction Step:		
Friedel-Craft acylation	Reactant A:	Isobutylbenzene (IBB)
	Reactant B	Acetic anhydride
	Main Product	4-Isobutylacetophenone
	Side Products	2-isobutylacetophenone; acetic acid; acetyl fluoride
	Phases	IBB rich phase-HF rich phase
	Solvent	HF
	Solvent Role	Product extraction
	Catalyst	HF (Acid source)
	Reaction conditions	T = 80^{o}C; P =0.7 MPa; t = 3 hr
	Reaction data	X_{IBB} = 85%; S_{IBAP} =81%
	Experimental data	Starting and end points
	Scale	Lab scale
	Models	Not available

Reaction Step 2. Hydrogenation

The second reaction step is a hydrogenation step where the produced 4-IBAP from the first reaction step reacts with hydrogen (H_2) in the presence of hydrogen catalyst to form 1-(4´-isobutylphenyl) ethanol. The hydrogenation reaction is a heterogeneous multiphase catalytic reaction which involves three phases (gas-liquid-solid). The hydrogenation catalyst might be Pd/C or Raney Nickel which is insoluble in reaction phase and it can be easily recovered and re-activated [38], [183]. The reaction is a solvent-free reaction, but solvent can also be used to bring the reactants together and decrease the overall reaction time. For the analysis and reaction optimization, available data and kinetic models are available. The reaction data has been retrieved using the reaction type database is given in Table 5.2.

Table 5.2 Prelimenary data collected for the hydrogenation step.

Reaction Step:		
Hydrogenation	Reactant A:	4-isobutylacetophenone
	Reactant B	Hydrogen
	Main Product	isobutyl phenyl ethanol
	Side Products	p-isobutyl styrene, p-isobutyl ethyl benzene
	Phases	G-L-S
	Solvent	Solvent free or Methanol
	Solvent Role	Dissolve reactants
	Catalyst	See Table 5.3
	Reaction conditions	See Table 5.3
	Reaction data	See Table 5.3
	Experimental data	Dynamic data (concentration with respect time) for different reaction conditions
	Scale	Lab scale
	Models	Available

Table 5.3 lists different catalysts and the corresponding reaction conditions for the hydrogenation step as they have been reported in literature by different researchers and stored in reaction database.

Table 5.3 Hydrogenation Step: Review of different catalysts and solvents.

Catalyst	**Promoter**	**Solvent**	**T (K)**	**P_{H2} (MPa)**	**Conversion 4-IBAP (%)**	**Selectivity IBPE (%)**	**Yield IBPE (%)**	**Ref**
Pd/C	-	MeOH	303	0.68	99.5	96.6	-	[182]
Raney Ni	-	-	353	0.68	>99	98	-	[182]
Pd/C	aq. NaOH	-	298	0.86	99.5	-	92	[182]
10% Ni/HY	NaOH	MeOH	393-413	5.7-5.9	75	75	-	[184]
Ru/Al_2O_3	-	MeOH	373-398	3.4-6.2	76	60	45	[32]
Pd black	-	Cyclohexane	373	2	90	58	52	[33]
Pd/SiO_2	-	n-Decane	373	2	90	69	62	[34]
Pd/SiO_2	-	n-Decane	373	1	90	80	72	[185]
Pd/C	NaOH	EtOH	343	2	100	96.4	96.4	[186]

Reaction Step 2. Carbonylation

To convert the produced 1-(4′-isobutylphenyl) ethanol to the final product, ibuprofen, and a carbonylation reaction step is used. The reaction is a three phase reaction (G-L-L) where the reactants and products form the organic phase, the catalyst and the acidic promoters are in the aqueous phase and finally carbon monoxide is in gas phase. The reaction is a solvent-free reaction and it is taking place above the melting point of the organic compounds, solvent can also be used in order to bring the reactants together and to finally increase the reaction rate. The collected data has been retrieved from the reaction type database is given in Table 5.3.

Table 5.4 Prelimenary data collected for the carbonylation step.

Reaction Step:		
Carbonylation	Reactant A:	isobutyl phenyl ethanol (IBPE)
	Reactant B	CO
	Main Product	Ibuprofen
	Side Products	Isobutyl styrene (IBS), 1-(4-isobutylphenyl)-ethyl chloride (IBPCl), 3-(4'-isobutyl phenyl) propionic acid
	Phases	G-L-L
	Solvent	Solvent free or MEK
	Solvent Role	Dissolve reactants
	Catalyst	$PdCl_2/PPh_3$
	Reaction conditions	T = 110-140ºC; P =5-16.5 MPa; t = 2-4 hr
	Reaction data	X_{IBPE} > 99%; S_{IBU} =96-98%, S_{IPPA} =1.00%, S_{IBPCl}=1.00%, S_{IBS}=0.2%
	Experimental data	Dynamic data (concentration with respect time) for different reaction conditions
	Scale	Lab scale
	Models	Available

Step B.2. Perform kinetic study

The *Friedel-Craft acylation* is classified as a reaction class type C as the reaction time is above 10 min. Mass transfer limitations do exists because of the low solubility of IBB in HF [187], therefore rigorous mixing is required to bring the reactants in contact. Dynamic data is not available and kinetic model has not been developed, therefore, the analysis of the reaction is based on published experimental results, which have been stored in reaction type database.

The *Hydrogenation reaction* is classified as a reaction class type C, the mass transfer of hydrogen to the organic phase is the main limitation, which also controls the mechanism of the reaction. Therefore, a rigorous mixing is required to overcome this limitation. Dynamic data sets for different cases of 4-IBAP hydrogenation to IPBE at different conditions is available in literature. Kinetic models have also been developed and published and they can be used to fit and validate the experimental data.

The *Carbonylation reaction* is classified as a reaction class type C. In this reaction, the mass transfer of carbon monoxide in the organic liquid phase and then reaction at the interface of organic-aqueous phase are the main limitations. Rigorous mixing and high partial pressure of carbon monoxide are required to overcome these limitations. Dynamic data for the carbonylation step is available and kinetic models published in literature have been used to fit and validate the experimental data.

The main results from the kinetic study are given in Table 5.5,

Table 5.5 Kinetic study for the three reaction steps.

Reaction Step:	**Reaction S.1**	**Reaction S.2**	**Reaction S.3**
Reaction Class [166]	Slow C	Slow C	Slow C
Mass Transfer	Mass Transfer Limitation	Mass Transfer Limitation	Mass Transfer Limitation
Heat Transfer	no	Highly exothermic	no
Equilibrium	No information	No information	No information
Control Mechanism	Mass Transfer	Mass transfer and kinetics	Mass transfer and kinetics
Kinetic model	Not available	Fitted and validated	Fitted and validated

In Figure 5.3 the kinetic model fitting in experimental data is illustrated. The kinetic model development is based on published kinetic models, hydrogenation step [34] and carbonylation step [37]. Model analysis and parameter estimation based on published data from different research groups has been performed in both models. In Figure 5.3, the fitted hydrogenation and carbonylation kinetic model for different sets of experimental data is illustrated.

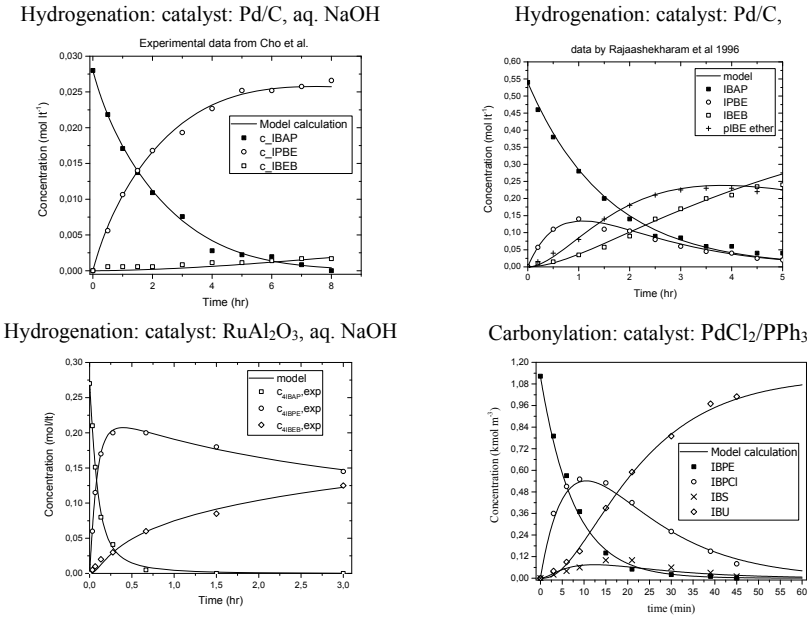


Figure 5.3 Fitted kinetic model for the hydrogenation and carbonylation steps.

Step B.3 Evaluate Process Variables

Reaction Step 1. Temperature is an important parameter for the Friedel-Craft reaction as a low boiling point solvent is used (HF). The reaction takes place in temperature between 45-80^{o}C and high pressure is used to prevent hydrogen fluoride to vaporize. Rigorous mixing is required as IBB is slightly soluble with HF and it needs to be in contact with the acetylating agent, which is soluble in HF [187], [188]. Because of the lack of detailed reaction information such as experimental data and/or a validated kinetic model, the process variables evaluation is restricted to observations during the experimental analysis and process concerns.

Reaction Step 2. To evaluate the reaction process variables for the hydrogenation reaction step the reaction kinetic model is used for simulation under different reactions conditions. Using simulations, the reaction variables such as temperature, concentration, pressure are evaluated using sensitivity analysis, as shown in Figure 5.4 and Figure 5.6. The amount of catalyst is crucial for the process as for higher amount (see Figure 5.4b) the reaction rate is high. However, the operation process space that the selectivity to the desired product is at the maximum value is very narrow (see Figure 5.4b) compare to the wider operational window obtained when lower amount of catalyst is used (see Figure 5.4a).

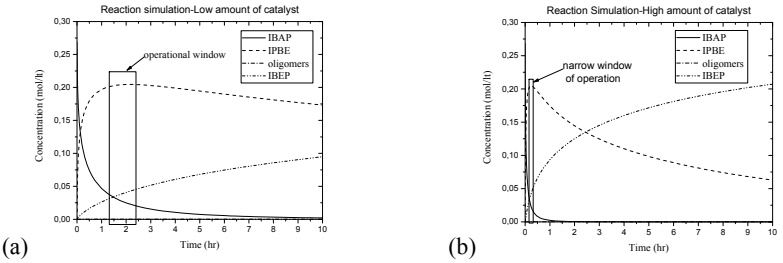


Figure 5.4 Simulation of the reaction performance for different amount of catalyst.

The initial concentration of IBAP also affects the reaction rate; the reaction becomes slower for higher concentrations of IBAP (see Figure 5.5a). It has been also shown that the absence of water is important for the reaction as increase concentration of water increase the production of oligomers (see Figure 5.5b).

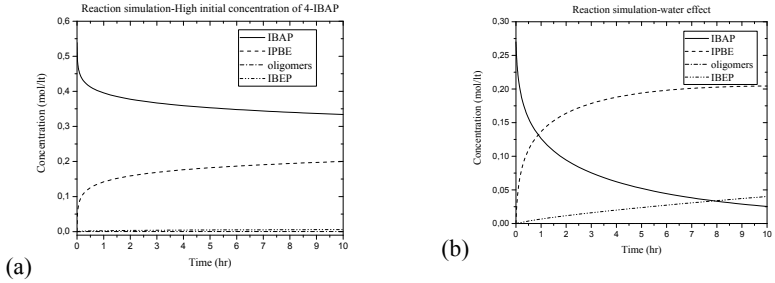


Figure 5.5 Reaction simulation for higher initial concentration of IBAP (a) and presence of water in the initial mixture (b).

High operation temperature results higher production of by-products and lower temperature results in very low reaction rate where the conversion of the reactant is not sufficient high (see Figure 5.6b). As shown in Figure 5.6c the partial pressure of hydrogenation affects the reaction rate, for low pressure the reaction rate is very slow resulting in very low conversion and selectivity, at higher pressures the conversion and the by-products production are increasing.

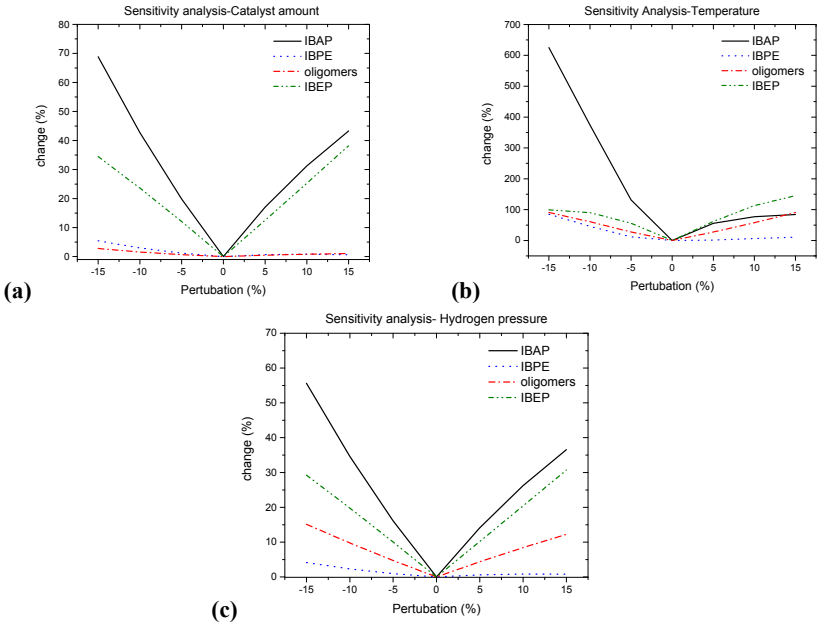


Figure 5.6 Sensitivity analysis of the reaction variables (amount of catalyst (a), temperature (b), partial hydrogen pressure (c)) for the hydrogenation step.

After the analysis of the reaction variables for the hydrogenation step it can be seen that using the system with $RuAl_2O_3$ the high selectivity of the desired product cannot be achieved. However, using the system with Pd/C catalyst and NaOH as it can be seen the high selectivity and high conversion can be achieved and the same reaction model can be used for the evaluation of the reaction variables. Using Raney nickel catalyst the performance of the reaction is similar or better that using Pd/C and aq. NaOH and less harsh conditions are used (lower pressures and lower temperatures). Unfortunately, dynamic data is not available when Raney nickel catalyst is used. Raney nickel catalyst is selected for further evaluation because the better reaction performance compare to the other catalyst systems used in different research articles. In case that, dynamic data becomes available, the kinetic model, used for the hydrogenation step can be used to fit the experimental data and used for optimization studies.

Reaction Step 3. The final carbonylation step has been evaluated similarly to the hydrogenation step. High reaction temperatures increase the reaction rate and the yield to the desired product Figure 5.7a while lower temperature results to lower reaction rate and longer reaction times

(see Figure 5.7b). Low partial pressures of CO decreases the reaction rate and the yield to the desired product whereas higher pressures increase the reaction rate and the yield (see Figure 5.7c). The concentration of catalyst (see Figure 5.7e), promoters (see Figure 5.7d) and the concentration of water (see Figure 5.7f) affects the reaction rate and the yield to final product. The results are illustrated in detail in Figure 5.7.

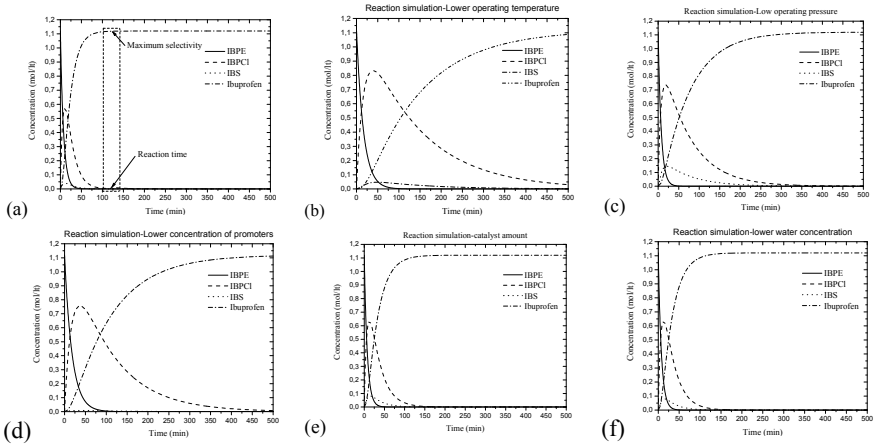


Figure 5.7 Reaction simulation for the carbonylation reaction under different process conditions. Plot (a) Reaction conditions used by [182] given in Table 7.5, the changes corresponding to each case are: plot (b) T = 80 ^{o}C, plot (c) P_{CO} = 1 bar, plot (d) promoters concenrtation 0.121 mol/lt, plot (e) 1.124 x 10^{-3} mol/lt and plot (f) c_{H2O} =0.1 mol/lt.

Table 5.6 gives the summary of the evaluation of the process variables, which affect the each reaction step and the decision in the process conditions.

Table 5.6 Evaluation of process variable for all the reaction step to produce ibuprofen.

Variable	**Reaction S.1**	**Reaction S.2**	**Reaction S.3**
Temperature	45-80^{o}C	High Temperature by-products yield is higher, low temperature the reaction rate is low	High Temperature increases the yield
Mixing	Rigorous	Rigorous	Rigorous
Concentration	no information	Concentration of water increases the oligomers	High Concentration of catalyst, substrate and promoter, yields to higher reaction rates
Stoichiometry	Excess of HF and Reactant (Ac_2O)	no information	no information

Pressure	High pressure to prevent mixture from boiling	High pressure of H_2 increases the selectivity	High pressure P_{CO}
pH	Acidic environment	no information	Acidic environment
Decision on reaction conditions:			
Reaction Conditions	**T = 80°C P = 0.7 MPa t= 3 hr**	**T = 30°C P_{H2} = 0.7 MPa t = 2 hr**	**T = 120°C P_{CO} = 5.4 MPa t = 2 hr**
Reaction Performance:			
	C: 85% S: 81%	C: 99.5% S: 98 %	C: 100% S: 98%

Step B.4 Batch or continuous?

Reaction step 1: The Friedel-Crafts reaction is a reaction that can be benefit from in continuous mode, the mixing is going to be improved, and the recycle of unreacted IBB and HF can be facilitated. The reaction system consist of two phases, the IBB rich phase, and the HF rich phase. The HF-rich phase contains the acetylating agent and the produced product that is selectively dissolved in HF phase. By searching in the unit operation database, reactions of this type can be operated in a counter-current plug flow reactor with or without packing material. In this way, the reaction will take place and at the same time, the phases are separated. Then, the unreacted IBB can be recycled back while the HF-rich phase, which contains the main product and the acetylating agent, is a subject of further separation to separate the product from HF and acetylating agent. In this way, the solvent can be fully recovered and recycled back in the reactor.

Reaction step 2: Continuous operation can be beneficial for the hydrogenation reaction as the mass transfer of the gas phase to the organic phase can be enhanced. Moreover, the selectivity towards the product reaches a maximum after some time and the decreases rapidly. The use of continuous mode can also ensure constant product quality. Using the unit operation database, a reaction like this can be operated in reactors such as fixed bed reactor or trickle-bed reactor where the catalysts resides in the reactor.

Reaction step 3: For the carbonylation step, continuous mode can also be beneficial for the process as it will improve the mass transfer and it will allow higher carbon monoxide partial pressures. Using the unit operation database, a reaction like this can be operated in reactors such as plug flow reactor, or microreactors.

For this case study, the following decisions are made:

a. Continuous plug flow reactor, Lindley et al. [187]
b. Fed batch reactor
c. Fed batch reactor

Table 5.7 lists the potential benefits of continuous operation for the reactions required for ibuprofen synthesis. Table 5.7 also lists the possibilities of continuous reactors that might be applied for the specific reaction type and the final decision.

Table 5.7 Batch to continuous reaction for ibuprofen production process.

Step B.4. Batch or Continuous?	**Reaction S.1**	**Reaction S.2**	**Reaction S.3**
	Beneficial: a. Improved mass transfer, b. Recycle of HF, acetylating agent c. Recycle of IBB	Beneficial: a. Improved mass and heat transfer, b. Higher hydrogen pressure c. Recycle of solvent (if used)	Beneficial: a. Improved mass and heat transfer, b. Higher CO pressure c. Recycle of solvent (if used)
Unit Operation database	Two-phase plug flow reactor	Trickle-bed reactor or plug flow reactor	Continuous plug flow reactor or microreactor
Decision	Continuous	Fed-batch	Fed-batch

Step B.5. Reactor Design

The design of the reactors is based on simple design equations that are based on the residence time (or reaction time for batch reactions) and the flowrate (or the maximum amount). Table 5.8 gives the calculated volume of the reactor involved in ibuprofen synthesis.

Table 5.8. Reactor design for Ibuprofen synthesis.

	Friedel Crafts	**Hydrogenation**	**Carbonylation**
Operation	**Continuous**	**Fed-Batch**	**Fed-Batch**
Mixture density ($kmol/m^3$)	345	0.49	19.8
Reaction time (hr)	2	3	2.6
Total number of moles (mol)	82	588	756
Volume (m^3)	0.005	1.2	0.04
Safety factor	30%	30%	30%
Reactor Volume (m^3)	**0.0065**	**1.56**	**0.52**
Number of reactors	1; PFR	1; Batch	1; Batch
Total operation time[*,**]	1 day	5hr	5.6hr

*For the flow reactor, it was assumed 1 day operation in order to produce sufficient amount of 4IBAP to eventually produce 75kg of Ibuprofen. ** The total batch time includes 1 hr filling time; 0.5 hr heating time; the reaction time; 0.5 hr cooling time and 1 hr emptying and washing time.

Step B.6. Is separation required?

Reaction step 1: Separation is required after the first reaction step; the product stream consists of HF, product, and acetylating agent. HF needs to be separated and recycled back in the reactor in order to avoid any disposal to the environment of this not environmentally benign solvent. The acetylating agent needs to be separated and returned to the reaction and finally the product has to recover in a good purity for the next reaction step.

Reaction step 2: Separation is required to remove the hydrogen and the catalyst, the later needs to be recovered, regenerated, and reused. The by-products from the reaction need to be removed as well.

Reaction step 3: Separation is required for the last reaction step to remove carbon monoxide, the aqueous phase with the catalyst and the promoters and finally to purify ibuprofen from the impurities.

Table 5.9 lists the objectives of the separation for each reactive step.

Table 5.9. The separation objective for each reactive step of Ibuprofen's synthesis.

Reaction step	Separation?	Objectives
Friedel crafts	Yes	Hydrogen fluoride recovery and recycle Acetylating agent needs to recovered and recycled Product must be purified
Hydrogenation	Yes	Hydrogen Catalyst By-products separation
Carbonylation	Yes	CO Water phase Catalyst Product purification

After the reaction analysis in section B, the proposed production process for ibuprofen is illustrated in Figure 5.8.

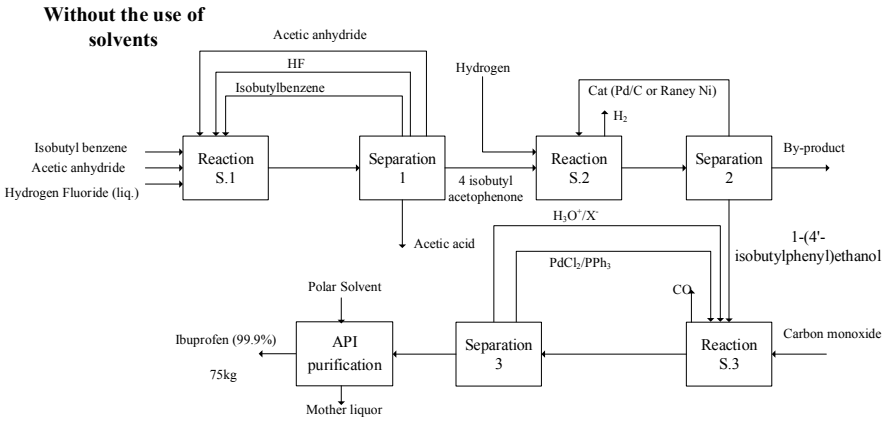


Figure 5.8 Production process of Ibuprofen based on the information obtained using Section B.

5.1.4 Section C. Separation synthesis

In this section, the objective is to generate separation processes to achieve the objectives defined in Step B.6. To determine the separation process a detailed analysis is required, therefore, the analysis and the results for Steps C.1-C.2 are illustrated in detail using one reaction step. For the rest of the reactive steps, the main output is going to be illustrated while the detailed analysis is given in Appendix A (Table 7.1-Table 7.5).

Step C.1. Mixture Analysis

The mixture analysis for the Friedel-Crafts acylation and the Hydrogenation reactive step is illustrated in Appendix A. The application of the steps C.1-C.2 is highlighted in detail through the carbonylation reaction step of ibuprofen synthesis. Table 5.10 lists the compounds after the carbonylation reaction has been completed, the role of the compound during the reaction and in which phase they are after the end of the reaction. Note, that in the analysis the catalyst and the promoters are not directly considered as they are soluble in water and it is considered that they are going to be separated together with the aqueous phase.

Table 5.10 Description of the compound involved in the carbonylation reaction

Component		Formula	Role	Phase
Carbon monoxide	(A)	CO	Reactant	Gas
Water	(B)	H_2O	Solvent	Aqueous (with aqueous soluble compound)
IPBE	(C)	$C_{12}H_{18}O$	Reactant	Organic
IBU	(D)	$C_{13}H_{18}O_2$	Main Product	Organic
IPPA	(E)	$C_{13}H_{18}O_2$	By-product	Organic
IBS	(F)	$C_{12}H_{16}$	By-product	Organic

The pure compound properties are listed in Table 5.11, where the properties of the compound in bold have been retrieved from CAPEC database. The pure compound properties of the rest have been estimated using ICAS-ProPred and have been stored in CAPEC database.

Table 5.11 Pure compound properties for the compounds involved in the carbonylation step.

	MW (gr/mol)	T_b (K)	T_m (K)	SolPar ($Mpa^{½}$)	H_{fus} (kJ/kmol)	P_{vap} (kPa)	RG (Å)	M_v (m3/mol)
CO	28.01	81.65	68.15	6.04	740.98	4000*	0.558	0.03
Water	18.00	373.15	273.15	47.81	6001.70	3.54	0.62	0.02
IPBE	178.28	538.74	295.26	19.51	16800.00	0.00	0.00	0.19
IBU	206.28	588.00	348.40	20.20	21900.00	0.00	5.76	0.20
IPPA	206.28	591.37	347.25	21.48	21320.00	0.00	0.00	0.21
IBS	160.25	524.00	231.17	18.05	13370.00	0.01	5.10	0.18

*at T= 130K

The binary ratio matrix is given in Table 5.12. According to Jaksland et al. [163] and Tula et al. [164], based on the created binary ratio matrix the feasible separation tasks can be identified.

Table 5.12 Binary ratio matric for a select set of properties.

Binary	MW	T_b	T_m	SolPar	H_{fus}	P_{vap}	RG	M_v
IPBE/IBU	1.16	1.09	1.18	1.04	1.30	9.33	1.03	1.04
IPBE/IPPA	1.16	1.10	1.18	1.10	1.27	∞	1.43	1.10
IPBE/Water	9.90	1.44	1.08	2.45	2.80	12633.74	1.13	10.46
IBU/IPPA	1.00	1.01	1.00	1.06	1.03	∞	1.47	1.05
IBU/Water	11.46	1.58	1.28	2.37	3.65	117914.94	1.16	10.88
IPPA/Water	11.46	1.58	1.27	2.23	3.55	∞	1.27	11.47
IBS/IPBE	1.11	1.03	1.28	1.08	1.26	18.67	1.09	1.04
IBS/IBU	1.29	1.12	1.51	1.12	1.64	174.22	1.07	1.08
IBS/IPPA	1.29	1.13	1.50	1.19	1.59	∞	1.57	1.14
IBS/Water	8.90	1.40	1.18	2.65	2.23	676.81	1.24	10.10

Based on the binary ratio matrix, the identified separation tasks for each binary pair are listed in Table 5.13.

Table 5.13 Identified separation tasks for the separation of the reaction mixture after the carbonylation step.

Binary pair	Separation tasks
IPBE/IBU	Crystallization, distillation, prevaporation,
IPBE/IPPA	Crystallization, distillation, prevaporation
IPBE/Water	Liquid-liquid phase separation
IBU/IPPA	solvent crystallization,
IBU/Water	Liquid-liquid phase separation
IPPA/Water	Liquid-liquid phase separation
IBS/IPBE	Crystallization, distillation,

IBS/IBU	Liquid membrane, prevaporation, crystallization,
IBS/IPPA	Liquid membrane, prevaporation,
IBS/Water	Liquid-liquid phase separation

Based on the identified separation tasks, the selected process groups are listed in Table 5.14.

Table 5.14 Generated process groups for the separation of the carbonylation raction mixture. The chemical species CO, water, IPBE, IBU, 3-IPPA and IBS are represnted with A-F respectively.

Process groups				
crDE/CF	crDEC/F	crC/F	crD/CF	fA/BCDEF
dsDE/CF	dsDEC/F	dsC/F	dsD/CF	rABCDEF
lmDE/F	lmD/F	lmE/F	dsDE/C	
pvDE/F	pvD/F	pvE/F	pvC/E	
scD/SE	scD/SCEF	scD/SEF	crE/CF	
dsS/E	dsS/CEF	dsS/EF	dsE/CF	
lmS/E	lmS/CEF	lmS/EF	crDE/C	

Note: distillation (ds), crystallization (cr), flash (f), reaction (r), prevaporation (pv), solvent crystallization (sc), liquid membrane (lm)

Step C.2. Separation alternatives generation

The structurally feasible process alternatives for the carbonylation step are listed in Table 5.15 in the form of SFILES. The generated process alternatives marked with bold (number 2, 7, 8 in Table 5.15) have been described in literature by Elango et al. [182] and Zey et al.[189]. The later patent describes different methods to purify mixtures compromising ibuprofen after the carbonylation step.

Table 5.15 Structurally feasible process alternatives for the carbonylation step. The chemical species CO, water, IPBE, IBU, 3-IPPA and IBS are represnted with A-F respectively.

Rank	**Process Alternatives [SFILES]**
1	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(scD/SCEF)[(oD)](lmS/CEF)[1(oS)](oCEF)
2	**(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(scD/SCEF)[(oD)](dsS/CEF)[1(oS)](oCEF)**
3	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(crDE/CF)[(oCF)](scD/SE)(lmS/E)[1(oS)][(oE)](oD)
4	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(crDE/CF)[(oCF)](scD/SE)(dsS/E)[1(oS)][(oE)](oD)
5	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(crDEC/F)[(oF)](crDE/C)[(oC)](scD/SE)(lmS/E)[1(oS)][(oE)](oD)
6	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(dsDE/CF)[(oCF)](scD/SE)(lmS/E)[1(oS)][(oE)](oD)
7	**(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(dsDE/CF)[(oCF)](scD/SE)(dsS/E)[1(oS)][(oE)](oD)**

8	**(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(crDEC/F)[(oF)](crDE/C)[(oC)](scD/SE)(dsS/E)[1(oS)][(oE)](oD)**
9	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(crDEC/F)[(oF)](dsDE/C)[(oC)](scD/SE)(dsS/E)[1(oS)][(oE)](oD)
10	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(crDEC/F)[(oF)](dsDE/C)[(oC)](scD/SE)(lmS/E)[1(oS)][(oE)](oD)
11	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(dsDEC/F)[(oF)](crDE/C)[(oC)](scD/SE)(dsS/E)[1(oS)][(oE)](oD)
12	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(dsDEC/F)[(oF)](crDE/C)[(oC)](scD/SE)(lmS/E)[1(oS)][(oE)](oD)
13	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(dsDEC/F)[(oF)](dsDE/C)[(oC)](scD/SE)(dsS/E)[1(oS)][(oE)](oD)
14	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(dsDEC/F)[(oF)](dsDE/C)[(oC)](scD/SE)(lmS/E)[1(oS)][(oE)](oD)

Step C.3. Separation process selection

Now, the analysis continues showing the main results of the process alternatives for all the three reactive steps. The first step in the selection of the process is to select the flowsheet with the minimum number of unit operations.

Reaction step 1: The selected flowsheets for the Friedel-crafts acylation are listed in Table 5.16. After the reaction, the liquid-liquid separation between the IBB-rich phase and HF-rich phase is considered in all process alternatives. It can be seen from the list, that IBB has not been completely removed, as it is slightly soluble in HF. The sequence and the type of the remaining unit operations given in Table 5.16 are different.

Table 5.16 Selected process alternatives with the minimum number of unit operations for the reaction step 1 (friedel-crafts acylation) where A: HF, B: IBB, C: IBAP, D: AcOH, E: AcF, F: Ac_2O.

	Generated SFILES
1	(iB)(iAC)(rABC/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(dsAE/FBC)2[oFDBC](dsFDB/C) [oFDB][oC]
2	(iB)(iAC)(rABC/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(dsAEFD/BC)2[oBC](dsB/C)[oB][oC]
3	**(iB)(iAC)(rABC/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(dsA/BCDEF)2(dsEFD/BC)[oEFD][oBC](dsB/C)[oB][oC]**
4	(iB)(iAC)(rABC/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(dsAEFD/BC)2[oBC](crB/C) [oB][oC]
5	(iB)(iAC)(rABC/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(dsAEFD/BC)2[oBC](fB/C) [oB][oC]
6	(iB)(iAC)(rABC/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(prevA/BCDEF)2[oBCDEF](dsEFDB/C) [oEFDB][oC]

The flowsheet number 3 is the one described by Lindley et al. [187], after the liquid-liquid phase separation where most of IBB is separated from HF phase. Then, the volatile compounds HF and AcF are removed, in the next step, which is a vapour-liquid separation. In the next separation step, the product is separated from the rest of the mixture in distillation columns.

Reaction step 2: The selected process alternatives for the hydrogenation step are listed in Table 5.17. The state-task network 1, which has been described by Elango et al. [182] is listed in

Table 5.17, where the hydrogen is removed after the reaction, the catalysts is filtrated and the impurities are removed by distillation from the main product. An extra separation unit might be required depending on the amount of the unreacted IBAP in the mixture.

Table 5.17 Selected flowsheets with the minimum number of unit operations for the reaction step 2, where A: H_2, B: IBAP, C: IBEP, D:water, E: IBEB.

	Generated SFILES
1	**(iA)(iB)(rAB/pABCDE)(fA/DECB)(oDECB)(DE/CB)[oDE][oCB](C/B)[oC][oB]**
2	(iA)(iB)(rAB/pABCDE)(fA/DECB)(oDECB)(D/ECB)[oD][oECB](EC/B)[oB][oEC](E/C)[oC][oE]
3	(iA)(iB)(rAB/pABCDE)(fA/DECB)(oDECB)(D/ECB)[oD][oECB](EC/B)[oB][oEC]crys(E/C)[oC][oE]
4	(iA)(iB)(rAB/pABCDE) (fA/DECB)(oDECB)(DE/CB)[oDE][oCB](C/B)[oB][oC]crys(E/C)[oC][oE]
5	(iA)(iB)(rAB/pABCDE (fA/DECB)(oDECB)(DEC/B)[oDEC](D/EC)[oD][oEC](E/C)[oC][oE]
6	(iA)(iB)(rAB/pABCDE) (fA/DECB)(oDECB)(DEC/B)[oDEC](D/EC)[oD][oEC]crys(E/C)[oC][oE]
7	(iA)(iB)(rAB/pABCDE) (fA/DECB)(oDECB)(DEC/B)[oDEC](DE/C)[oDE][oC]

Reaction step 3: The selected process alternatives for the carbonylation step are listed in Table 5.18. The state-task network 2, which has been described by Elango et al. [182] is listed in Table 5.18, where the carbon monoxide is removed after the reaction, the catalysts is removed with the aqueous phase during the liquid-liquid phase separation and a solvent is introduced for the crystallization of the main product. The solvent is then recovered in a solvent recovery unit.

Table 5.18 Selected flowsheets with the minimum number of unit operations for the carbonylation step. The chemical species CO, water, IPBE, IBU, 3-IPPA and IBS are represnted with A-F respectively.

	Process alternatives [SFILES]
1	(rABCDEF)(fA/BCDEF)[(oA)](spB/CDEF)[(oB)](scD/SCEF)[(oD)](lmS/CEF)[1(oS)](oCEF)
2	**(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(scD/SCEF)[(oD)](dsS/CEF)[1(oS)](oCEF)**
3	(rABCDEF)(fA/BCDEF)[(oA)](spB/CDEF)[(oB)](crDE/CF)[(oCF)](scD/SE)[(oC)](lmS/E)[1(oS)](oE)
4	(rABCDEF)(fA/BCDEF)[(oA)](spB/CDEF)[(oB)](crDE/CF)[(oCF)](scD/SE)[(oD)](dcS/E)[1(oS)](oE)
5	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(dsDE/CF)[(oCF)](scD/SE)(dsS/E)[1(oS)][(oE)](oD)
6	(rABCDEF)(fA/BCDEF)[(oA)](spB/CDEF)[(oB)](dsDE/CF)[(oCF)](scD/SE)[(oD)](lmS/E)[1(oS)](oE)

Step C.4. Specification of the unit operations

The specification of the separation factors for each unit operations have been selected by analysing the phase equilibrium diagrams (VLE, LLE, and SLE) for the compounds to be separated. The equilibrium calculations are performed in ICAS platform using the original UNIFAC for VLE, LLE, and NRTL-SAC for SLE calculations. Table 5.19 lists the process specifications and the process conditions for the unit operations for Ibuprofen synthesis for selected process alternatives (alternative 3 for Friedel Crafts step, Table 5.16; alternative 1 from the hydrogenation step Table 5.17; and alternative 2 for the carbonylation step see Table 5.18).

Reaction *step 3:* The selected process alternatives for the carbonylation step are listed in Table 5.18. The state-task network 2, which has been described by Elango et al. [181] is listed in Table 5.18, where the carbon monoxide is removed after the reaction, the catalysts is removed with the aqueous phase during the liquid-liquid phase separation and a solvent is introduced for the crystallization of the main product. The solvent is then recovered in a solvent recovery unit.

Table 5.18). The specifications are presented in terms of separation factors (ξ) between the pair of the separation. For example, if CA/B is a distillation separation and ξ_1=0.99 and ξ_2=0.01 it means that 100% of C, 99% of A and 1% of B are recovered as top product. The remaining is recovered as bottom product.

Table 5.19 Specifications of the different unit operation involved in Ibuprofen synthesis. Friedel-crafts acylation: alternative 1 see (Table 5.16), Hydrogentaion reaction: alternative 1 (see Table 5.17), carbonylation reaction: alternative 2 (see Table 5.18).

Reaction Step	Unit operation	Process Conditions	Separation factor	Solvent
Friedel-Crafts	L-L separation (A/B)	T = 348K, 7 atm	ξ=0.88*; ξ=0	-
	Distillation (E/F)	T = 298 K, 1 atm	ξ=0.99; ξ=0.01	-
	Distillation (	T = 298 K, 1 atm	ξ=0.99; ξ=0.01	-
	Distillation	T = 298 K, 1 atm	ξ=0.97; ξ=0.03	-
Hydrogenation	Flash	T = 310 K, 1 atm	ξ=1; ξ=0	-
	Filtration	T = 310 K, 1 atm	ξ=1; ξ=0	-
	Distillation	T = X K, X atm	ξ=0.99; ξ=0.01	-
Carbonylation	Flash	T = 390 K, 1 atm	ξ=1; ξ=0	-
	Liquid phase separation	T = 350 K, 1 atm	ξ=0.92; ξ=0	-
	filtration	T = 350 K, 1 atm	ξ=1; ξ=0	-
	Solvent Crystallization	T = 298 K, 1 atm	Table 5.18	Table 5.18
	Drying	T =$T_{b.solvent}$, 1 atm	ξ=1; ξ=0	-
	Solvent Recovery	Depends on the selected solvent	ξ=0.999; ξ=0.001	-

*The separation factor was calculated from data available in the patent [187]

Solvent is required only for the final purification of ibuprofen in a solvent crystallization operation. The solvents, which have been found in literature, are listed in Table 5.20, 2-ethoxyethyl acetate has been selected using computer-aided molecular design (CAMD) in ICAS platform and verified by experiments while the rest have been used in experimental studies first. As it is listed in Table 5.20, the values of potential product recovery (PR%) of the listed solvents are close to each other and the only mainly difference is on the crystal shape. Higher values of potential recovery are achieved when n-hexane or methanol are used and the lower PR value is obtained while the selected solvent through CAMD is used. However, even the slightly lower potential recovery, the overall process performance (consisting the next processing steps) might be improved because of the higher aspect ratio crystals obtained (experimentally verified by [130]) using the CAMD solvent.

Table 5.20 Maximum potential recovery, crystals shape and LC50 of Ibuprofen in different solvents, SLE equilibrium is illustrated in Figure 7.4 in Appendix A.

Solvent	PR%	Crystal shape	-log(LC_{50})
n-Hexane	96%	Needle-like [128]	3.54
n-Heptane	94%	Needle-like	3.83
n-pentane	93%	Needle-like	3.25
methanol	96%	Plate-like [128]	1.68
2-ethoxyethyl acetate	89%	Needle-like (higher aspect ratio) [128]	3.28

Step C.5. Batch or continuous?

According to Table 5.19, 15 unit operations are involved in the production of ibuprofen through the BHC pathway with the recycle. The first reaction step is performed in continuous mode, the separation process consist of three distillation processes. Distillation operation is compatible with the continuous mode and as long as the reaction runs in a continuous mode, the separation can be in continuous mode. The unit operations used after the second and third batch reactive steps are mainly in batch mode. Despite the crystallization, filtration and drying steps the rest of the separation steps are compatible with continuous operation. In addition, using the unit operation database the crystallization process can be performed in mixed suspension mixed product removal.

Table 5.21 Specifications of the different unit operation involved in Ibuprofen synthesis.

Reaction Step	Unit operation	Batch or continuous?
Friedel-Crafts	Distillation	Semi-continuous
	Distillation	Semi-continuous
	Distillation	Semi-continuous
Hydrogenation	Flash	Batch
	Filtration	Batch
	Distillation	Batch
Carbonylation	Flash	Batch
	Liquid phase separation	Batch
	filtration	Batch
	Crystallization	Batch
	Drying	Batch
	Solvent Recovery	Batch

Step C.6. Design of separation unit

In this case study, the step C.6 is not considered.

5.1.5 Section D. Process analysis/simulation and analysis

The process for the production of ibuprofen has now been obtained using the three first sections (A, B and C) of the developed framework. The next step is to validate the obtained process and perform process evaluation, identify optimization targets and define optimization objectives and finally propose the process operation.

The obtained flowsheet is illustrated in Figure 5.9. It consists of the continuous part for the synthesis and separation of the first intermediate and the state-task network for the hydrogenation, the carbonylation and the purification part. The continuous part, consists of the reactor and a liquid-liquid phase separation, the striping scetion to remove HF and AcF, the distillation to remove acetic acid and finally, a vacuum distillation to remove the impurities from the product. Then, the product of the first step is transferred to the second reactor, once the hydrogenation reaction is completed, the catalyst is separated from the mixture and the impurities are removed using a distillation under vaccuum. In the final step, the product of the second step reacts with carbon monoxide, then the CO is removed, the two liquid phases are separated and the product is purified (see Figure 5.9).

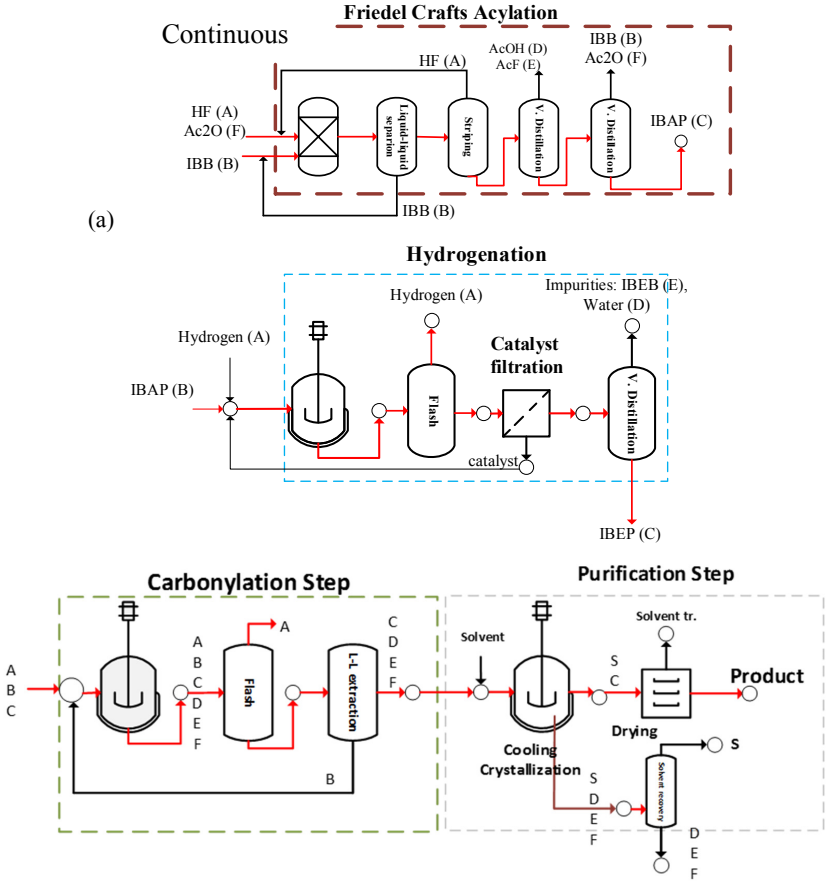


Figure 5.9 Obtained process for the production of ibuprofen through BHC pathway, (a) continuous friedel crafts acylation process; (b) state task network for the hydrogenation step and (c) is the state task network for the carbonylation step.

Step D.1. Process Simulation and Evaluation

The validation of the obtained process has been performed using the ICAS simulation tool. The operational scenario considered for comparison of key performance criteria are listed in Table 5.22.

Table 5.22 Defined scenario for ibuprofen simulation.

Scenario	Objective
Scenario A	Evaluate the alternatives for the third carbonylation step with respect to energy required per kg of product
Scenario B	Evaluate the key performance criteria of the carbonylation using different crystallization solvents

Process Simulation: Scenario A

The objective of the simulation scenario A, is to compare the process alternatives for the carbonylation and purification step in terms of energy. The results are given in Table 5.23, and as it can be seen that the process alternative "1" compared to the rest of generated process alternatives and it requires the least amount of energy per kg of pure product. For the process simulation, hexane was selected as a solvent for the crystallization step. The main difference of the first and the second alternative is that the solvent recovery step takes place in liquid-liquid membrane and not in a distillation.

Table 5.23 Process alternatives, evaluated through process simulation to investigate the energy saving during the practices.

Rank	Process alternatives [SFILES]	E
1	(rABCDEF)(fA/BCDEF)[(oA)](spB/CDEF)[(oB)](scD/SCEF)[(oD)](lmS/CEF)[1(oS)](oCEF)	1.2 MJ/kg
2	**(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(scD/SCEF)[(oD)](dsS/CEF)[1(oS)](oCEF)**	**+5%**
3	(rABCDEF)(fA/BCDEF)[(oA)](spB/CDEF)[(oB)](crDE/CF)[(oCF)](scD/SE)[(oC)](lmS/E)[1(oS)](oE)	+37%
4	(rABCDEF)(fA/BCDEF)[(oA)](spB/CDEF)[(oB)](crDE/CF)[(oCF)](scD/SE)[(oD)](dcS/E)[1(oS)](oE)	+44%
5	(rABCDEF)(fA/BCDEF)[oA)](spB/CDEF)(CDEF)(dsDE/CF)[(oCF)](scD/SE)(dsS/E)[1(oS)][(oE)](oD)	+125%
6	(rABCDEF)(fA/BCDEF)[(oA)](spB/CDEF)[(oB)](dsDE/CF)[(oCF)](scD/SE)[(oD)](lmS/E)[1(oS)](oE)	+124%

The detailed mass and energy balances have been performed in ICAS simulation tool, the detailed mass and energy balances for alternative "2" are given in Appendix A (Table 7.8-Table 7.10.). The process alternative "2" which is the current process has been selected for further evaluation.

Process Simulation: Scenario B

In this scenario, different solvents for the crystallization step are evaluated based on the analysis of the simulation results. Performance criteria such as the energy required/kg of product, the total solvent use, solvent use per kg of product, and waste generated per kg of product are evaluated. The results are illustrated Figure 5.10, where it is shown the normalized improvement of the process alternatives using different crystallization solvents. It can be seen that using methanol as the crystallization solvent the energy requirements are reduced while using 2-ethoxyethyl acetate the energy requirements are high compared to hexane due to the energy intensive . The total solvent use, has been improved by using 2-ethoxyethyl acetate, kg solvent/kg product has been improved significantly and finally the generated waste has been significantly improved by using either methanol or 2-ethoxyethyl acetate.

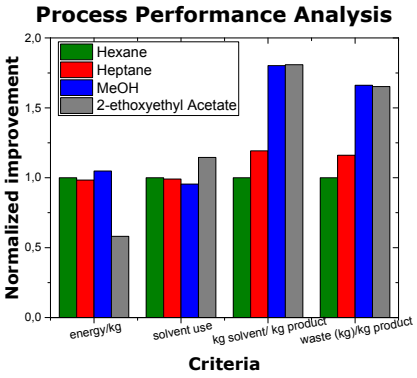


Figure 5.10 Perfomence criteria for the overall process to produce ibuprofen comparing four different crystallization solvents.

Environmental analysis using the WAR algorithm implemented in ICAS, has also been performed for the four different solvent it can be seen in Figure 5.11 that significant improvements can be achieved using 2-ethoxyetyl acetate. The environmental impact calculated using the WAR algorithm, first the impact of the inlet streams and then the impact of the outlet stream was calculated which subtracted from the impact of the inlet streams. Therefore, negatives values of environmental impact show improvement.

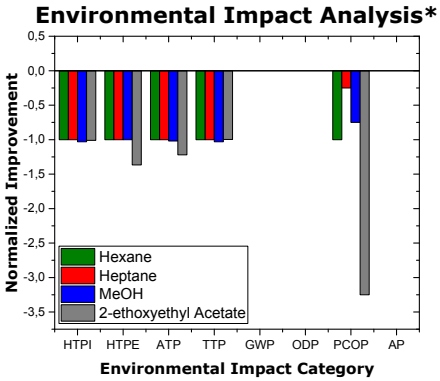


Figure 5.11 Normalized comparison of the enironmental impact of the process to produce iburpofen for four different crystallization solvents. HTPI: human toxicity potential by ingestion, HTPE: human toxicity potential by exposure, ATP: aquatic toxicity potential, TTP: terrestial toxicity potential, GWP: global warming, ODP: ozone depletion potential, PCOP: Photochemical oxidation potential and AP: acidification potential.

Considering the analysis for the crystallization solvents and that crystals with needle-like shape are preferred [128]–[130], 2-ethoxyethyl acetate is the best option as crystallization solvent. The weak point of using 2-ethoxyethyl acetate as a solvent is the energy requirements needed for the solvent recovery. The reduction of the energy required for solvent recovery can be subject of an optimization problem.

Step D.2. Process Optimization, control, monitoring, and validation

The section D, is not subject of this case study.

Step D.3. Process Operation

The process operation is not subject of this case study.

5.1.6 Conclusions

In this case study, the application of the overall framework was highlighted, all the section of except the Section D.2 and D.3 of the developed framework were verified. Reaction pathway was selected based on the evaluation of the proposed "green" metrics, reaction analysis was performed using model-based methods and experimental results, batch to continuous investigation was performed, process alternatives generated and process simulation and evaluation was performed comparing different process alternatives and crystallization solvents.

5.2 Case study 2: Solvent swap

The objective of this case study is to highlight the applicability of the developed solvent swap methodology through the systematic framework. The application of the framework is given in a summarized way while the focus has been shifted in the solvent swap methodology. For the application of the solvent swap methodology, four examples have been selected where the production process to produce the desired product is known. In all the cases, a solvent swap operation is needed to switch solvents. The first two examples deal with swap solvent selection for a given original solvent. In the first example, the swap solvent is used for solute recovery following the reaction, while in the second example; it is used for another reaction. The third example deals with the selection of an original solvent that is suitable for reaction task and verifies if it can be swapped by known swap solvent that is the best for the crystallization task following the reaction. Finally, the fourth example deals with the selection of a swap solvent that should first enhance the liquid-liquid phase separation after the reaction task, then replace the original solvent in a batch distillation operation and finally, be a good solvent for the subsequent crystallization step. The detailed application of the framework and the methodology is highlighted for example A while for the other examples, only selected issues of the solvent swap methodology are highlighted.

5.2.1 Example A. 6-Hydroxybuspirone Synthesis and purification

6-Hydroybuspirone is synthesized in one-step conversion from buspirone in tetrahydrofuran (THF). After the completion of the reaction, MTBE is added in reaction mixture to enhance the phase split between the organic (API, impurities) and the aqueous phase (catalyst and promoters). Finally, crystallization is employed in another solvent to isolate and recover 6-Hydroybuspirone from the organic mixture [190].

Problem Definition:

a. Selection and evaluation the performance of solvents in solvent swap operation.
b. Evaluation of the selected solvents performance in the crystallization unit.

Section A: Reaction pathway identification

Step A.1. Select API or intermediate: **6-Hydroybuspirone**

Step A.2. Reaction pathway identification: Using the reaction type database two pathways have been found, one is involving the oxidation of buspirone to 6-hydroxybuspirone [190] and the other one is involving the selective enzymatic reduction of buspirone to 6-hydroxybuspirone [191]. In this example, the process for the production of 6-hydroxybuspirone using the chemocatalytic way is fixed; therefore, the chemical synthesis is selected for further analysis. The reaction path is illustrated in Figure 5.12.

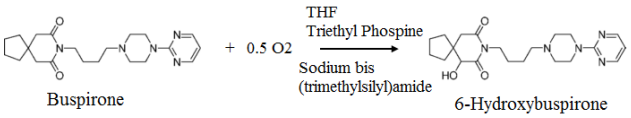


Figure 5.12 Reaction pathway from buspirone to 6-hydroxybuspirone [190].

Section B: Reaction analysis

The process involves the enolation of buspirone in tetrahydrofuran at very low temperature range of -68ºC to -75ºC in presence of excess of triethylphosphite (3.0-3.5 eq.). Then oxygen in form of air is added in the system for the oxidation of the formed enolate and reaction completion. The selected solvent is THF due to its good solubility of buspirone and 6-hydroxybuspirone during the reaction at low operating temperatures. The reaction temperature is low to ensure that the formed enolate will not be decomposed during the reaction. Enolate the thermally sensitive and due to the potential big temperature gradients (enolation step: exothermal reaction 41.9 kJ/mol, adiabatic temperature rise 4.2 ºC; oxidation step: exothermal reaction 685 kJ/mol, adiabatic temperature rise 68 ºC), every low temperature has been selected. Additionally, triethylphosphate low concentration leads to the formation of impurities, high concentrations of triethylphosphate lower the product recovery during the purification task. Regarding the process safety, at high concentrations of triethylphosphite, the consumption hazardous peroxides, which are formed as intermediate products, is ensured. Therefore, the build-up of these compounds in the reactor is minimized together with any potential risks [12], [190]. High concentration of the base and introduction of air, prior to complete enolation leads to the formation of diol by-product. Table 5.24 gives the summary of the reaction analysis section.

Table 5.24 Reaction analysis for the oxidation of buspirone to 6-hydroxybuspirone.

Reaction Step: Oxidation of buspirone		
Step B.1 Data collection	Reactants:	Buspirone; Oxygen
	Main Product	6-hydroxybuspirone
	Side Products	6,10-dihydroxybuspirone
	Phases	Organic phase
	Solvent	THF
	Solvent Role	Dissolves reactant
	Catalyst	Triethylphosphite
	Reaction conditions	T = -60ºC; P = 1atm; t = 8-24 hr
	Reaction data	Yield = 69-71%
	Experimental data	Starting and end points
	Scale	kg-scale
	Kinetic Models	Not available
Step B.2 Kinetic Study	Reaction Class	Slow C
	Mass Transfer	Mass Transfer Limitation
	Heat Transfer	Heat transfer limitation
	Equilibrium	No information
	Control Mechanism	Mass Transfer
	Kinetic model	Not available

Step B.3 Process evaluation	Temperature	-68ºC to -75ºC
	Mixing	Rigorous
	Concentration	
	Stoichiometry	Excess of triethylphosphite, stoichiometric amount of base
	Pressure	No information
	pH	-
	Solvent	THF
	Process conditions	T = -68ºC; P = 1 atm, t= 8-24hr
	Process performance	C=82%; S:high
Step B.4 Batch or continuous	Potential benefits	a. Improved mass and heat transfer, b. Improved process safety
	Unit operation database	Microreactor or trickle bed reactor
	Decision	Batch reactor (Process is fixed)
Step B.5 Reactor design		Not performed
Step B.6 Separation objectives		a. Purify product b. Remove triethyl phosphate c. Rremove sodium bis (trim- ethylsilyamide)

Section C: Separation synthesis

Steps C.1-C.3: The process for the separation of 6-hydroxybuspirone is fixed. Therefore, the steps C.1-C.3, to identify the type and the sequence of unit operations is not necessary to be performed. A simple state-task network is illustrated in Figure 5.13 [190].

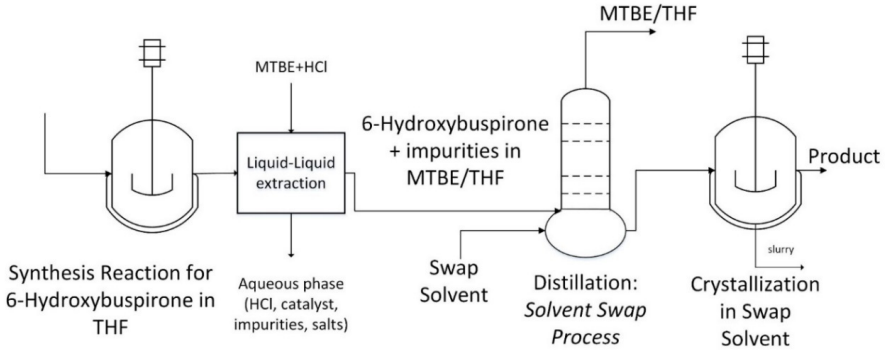


Figure 5.13 Processing tasks for case study 1: reaction in THF, phase separation assisted by MTBE addition, solvent swap, crystallization in the swap solvent.

Step C.4 Specification of unit operation

Table 5.25 lists the unit operations involved in the separation of the reaction mixture, the process conditions, the separation factors, and the solvent required for the separation. The conditions and the specifications for the solvent swap operation and the following

crystallization task depend on the selected swap solvent. For the swap solvent selection the developed solvent swap methodology is employed.

Table 5.25 Specifications of the different unit operation involved in 6-Hydroxybuspirone synthesis.

Reaction Step	Unit operation	Process Conditions	Separation factor	Solvent
Oxidation	Liquid-Liquid phase separation	T = 298 K, P = 1 atm	ξ=0.99; ξ=0.01	MTBE, aq. HCl
	Solvent swap operation	T, P	Depends on the selected solvent	Swap Solvent
	Crystallization	T = 298 K, P = 1 atm	Depends on the selected solvent	Swap solvent

Solvent swap methodology

Step 1. Problem definition: The objective of this case is to select a swap solvent to swap the original solvent (THF/MTBE) and maximize the product recovery in the crystallization task (see Figure 5.13).

Step 2. Feasible swap solvents candidates

The swap solvent needs to have higher boiling point than the original solvent, the relative volatility of the original solvent compared to the swap solvent needs to be high and preferably no azeotrope formation with the original solvent (Table 4.1). Using the swap solvent database (Figure 4.12 and Figure 4.13), the solvents satisfying these criteria are given in Table 5.26.

Table 5.26 Generated feasible swap solvent candidates by the step 2.1 of the method (see Figure 4.6), considering the good solvent swap.

Original solvent	Swap solvent candidate	$T_{b\ OS} << T_{b\ SwapS}$	Relative volatility	Azeotrope
THF	Acetic Acid	65<<117.9	10.12	No
	2-propanol	65<<82.2	3.44	No
	Toluene	65<<110.6	5.61	No
	Isopropyl Acetate	65<<88.6	2.65	No
	Anisole	65<<153.7	43.02	No
	Methyl isobutyl ketone	65<<116.5	7.97	No
	Ethyl Acetate	65<<77.1	1.71	No
	2-Methyltetrahydrofuran	65<<78	1.46	No
	Acetonitrile	65<<81.6	1.76	Yes
	Water	65<<100	6.60	Yes
	N,N-Dimethylformamide	65<<152	38.38	No
	N-Methyl pyrrolidone	65<<202	445.27	No
	Ethanol	65<<78.2	2.65	Yes
	1-butanol	65<<117.7	22.04	No
	2-methyl-1-propanol	65<<107.8	13.12	No

Note: subscript OS indicate original solvent; SwapS indicates swap solvent

The identified solvents given in Table 5.26 are further analysed considering the vapour-liquid equilibria phase analysis and investigating the vacuum effect in the system (see Figure 4.14). The results of the analysis are given in Table 5.27.

Table 5.27 Generation feasible swap solvent candidates by the Step 2.2 of the solvent swap methodology, considering the VLE analysis.

Original solvent	Swap solvent candidate	Solvent Swap Process Classification	Vacuum effect
THF	Acetic Acid	Very Easy	Positive
	2-propanol	Difficult	Positive
	Toluene	Easy	No effect
	Isopropyl Acetate	Difficult	Weakly positive
	Anisole	Very Easy	Positive
	Methyl isobutyl ketone	Very Easy	Weakly positive
	Ethyl Acetate	Very difficult	Weakly positive
	2-Methyltetrahydrofuran	Very difficult	No effect
	Acetonitrile	C10	No effect
	Water	C16	No effect
	N,N-Dimethylformamide (DMF)	Very Easy	Positive
	N-Methyl pyrrolidone	Very Easy	No effect
	Ethanol	C33	Positive
	1-butanol	Very Easy	Positive
	2-methyl-1-propanol	Very Easy	Positive

Step 3. Candidate analysis

The swap solvent must not only be able to replace the original solvent from the reactor effluent, but also must have very good performance during the next processing step, which is crystallization. Therefore, the aim here is to select a solvent from the list given in Table 5.27, which will lead to high product recovery from the crystallization task.

Model development – parameter regression

To evaluate the potential product recovery during crystallization in different solvents, a detailed analysis of solid solubility is required. Although ICAS-SolventPro can be employed to calculate the solid solubility, for the given API product, the model parameters for the NRTL-SAC model needs to be estimated first. As experimental solubility data of 6-hydroxybuspirone in 13 solvents are available [190], they are used for the parameter regression, where 8 solvents out of the 13 are used as representatives of hydrophilic, polar, hydrophobic solvents (experimental data is given in Table 7.11). The regression has been performed in ICAS-SolventPro and the regressed NRTL-SAC molecular parameters for 6-hydroxybuspirone from its solubility data in eight solvents are given in Table 5.28.

Table 5.28 Regressed NRTL-SAC parameters solute.

Segment Parameters	X	Y-	Y+	Z
6-Hydroxybuspirone	0.411	0.255	1.761	0

Solute solubility analysis and swap solvent selection

With the regressed parameters the NRTL-SAC model can be used to predict the solubility of 6-hydroxybuspirone in the remaining and other solvents. The predictions are shown in Figure 5.14 where the empty circles represent the solid solubility data in the eight pure solvents that were used for the regression step while the solid circles represent those that were not included. It is important to note that the model does quite well at the low solubility where the swap solvent should work and the high solubility where the original solvent should work.

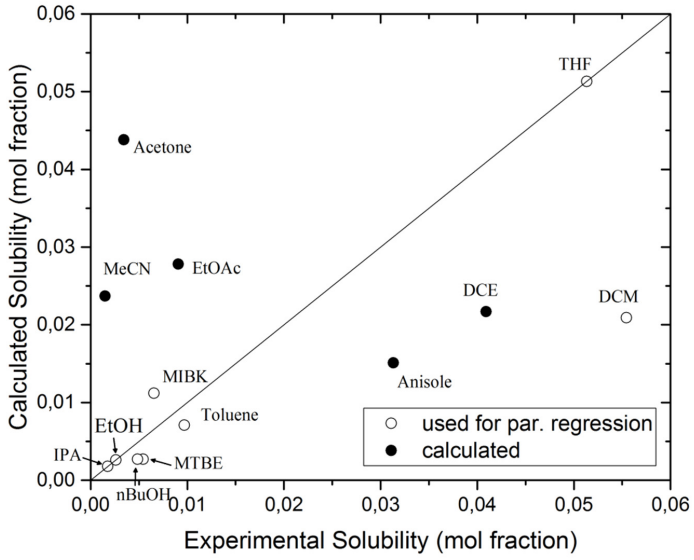


Figure 5.14 Regression of the NRTL-SAC parameters, empty circles indicate data used for regression and the filled ones are the predicted values.

The identified model is also used to predict solid saturation curves in different solvents as a function of temperature, which are shown in Figure 5.15. According to the data in Figure 5.15, 2-Propanol (IPA), Ethanol (EtOH) and 1-Butanol (n-BuOH) have the potential for high product recovery and are therefore, selected for further analysis.

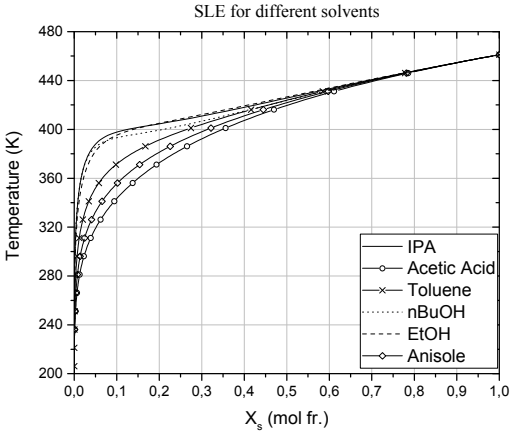


Figure 5.15 Solid-Liquid equilibria (SLE) of the solute with respect to the temperature for different solvents.

Identify operational limits for batch distillation

Detailed solubility analysis is performed to identify the solubility limits during the distillation operation to avoid solute precipitation during batch distillation. The solute solubility in the solvents as a function of temperature and solvent mixture is shown in Figure 5.16 for the IPA-THF solvent mixture. The results for the other two solvents (EtOH and n-BuOH) are included in Appendix B (see Figure 7.6 and Figure 7.8). Selecting a temperature below the saturation point guarantees that precipitation of the solute will not occur during the swap operation by batch distillation. The solid saturation curves help to establish the maximum potential recovery after each batch distillation run.

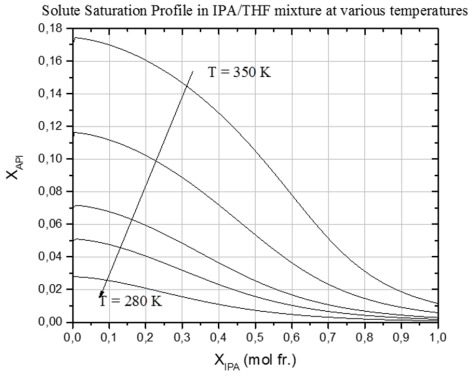


Figure 5.16 Saturation solubility of the solute as a function of the solvent mixture composition (IPA-THF) for different temperatures.

Section D. Process analysis/simulation and analysis

In this section, the identified swap solvents are going to be evaluated through dynamic simulations. Detailed calculations are considered for the solvent swap operation, and simple mass balances, based on the solid-liquid equilibrium, are considered for the crystallization operation. The simulation were performed in ICAS using the dynamic batch distillation tool, the results of the simulations used to evaluated the process alternatives based on the predefined criteria.

Step D.1 Process simulation/evaluation

Swap operation

The selected swap solvents are evaluated through rigorous dynamic simulations of batch distillation operations by using ICAS-still. The simulation results verify if feasible operational criteria such as operation time, swap solvent use, solvent water, and swap solvent charges can be obtained for the specified product recovery. Table 5.29 gives the details of the mixture (organic phase) after liquid-liquid extraction and before the swap operation.

Table 5.29 Mixture composition of organic phase after the liquid-liquid extraction task.

Compound	Amount, kg
MTBE	16.20
THF	165.29
Buspirone	2.65
6-Hydroxybuspirone	7.35
Diol	traces

Starting with the charge given in Table 5.29, 79 kg of fresh swap solvent are added to the batch distillation still. Dynamic simulations are performed for a boil-up flowrate of 1 kmol/hr and a still volume of 0.3 m^3 at a reduced pressure of 0.1 atm. The obtained simulation results are presented in Figure 5.17 where the simulated volumetric compositions in the batch still during the batch distillation operation are shown. As expected, the total volume of the still and the compositions of the original solvent (THF & MTBE) decreases during the operation while composition of the swap solvent increases. The end of the operation, as batch distillation limit, (see Figure 5.17) is identified as the composition of the solvent that is not high enough to prevent solute precipitation - detailed solubility analysis from step 3 (this calculation procedure is explained in detail in section B-I.1 of the Appendix B). Therefore, to avoid precipitation during swap operation, the batch distillation should be stopped at the distillation limit or more swap solvent should be charged. The composition at the end of batch distillation is given in Table 5.30

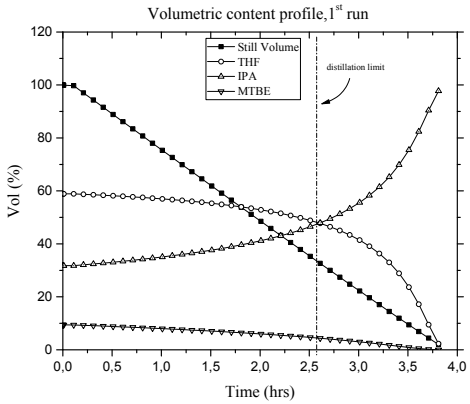


Figure 5.17 Simulated transient responses of volumetric compositions and the still volume in a batch still (ICAS-Batch Still used for simulation). The distillation limit represents the point where the operation has to stop in order to avoid solute precipitation.

Table 5.30 Final composition of the mixture after the end of the batch distillation.

	MTBE	IPA	THF	Product
Amount (kmoles)	0.0314	0.6787	0.6718	0.0204
mol fraction (mol%)	0.0224	0.4840	0.4790	0.0146
Mass fraction (wt%)	0.0272	0.3999	0.4749	0.0980

Product recovery by crystallization

The evaluation of the candidate swap solvents also need to consider the operational tasks after batch distillation. For example, if the product is to be recovered through crystallization, then the maximum potential for product recovery achievable through the swap solvent needs to be calculated apriori (see calculation example 1 in section B-I.2 in appendix B).

Another issue with respect to use of crystallization for product recovery is how many times the operation needs to be repeated to achieve a desired product recovery amount.

In Figure 5.18, t the initial (point 1), and the final (point 2) in terms of composition of the solute in the solvent mixture are shown as filled circles. The corresponding solute saturation curves for the initial and final compositions are also shown in Figure 5.18. It can be noted that by simply cooling from the final composition point to ambient temperature, no product can be recovered as solid. Only if the mixture is cooled further down to 285 K, around 30% of the product is recovered. Therefore, in order to achieve higher product recovery, additional solvent swap charges are needed to replace completely the original solvent. Another option is run a sequence of crystallization operations at different solvent concentrations and/or temperatures.

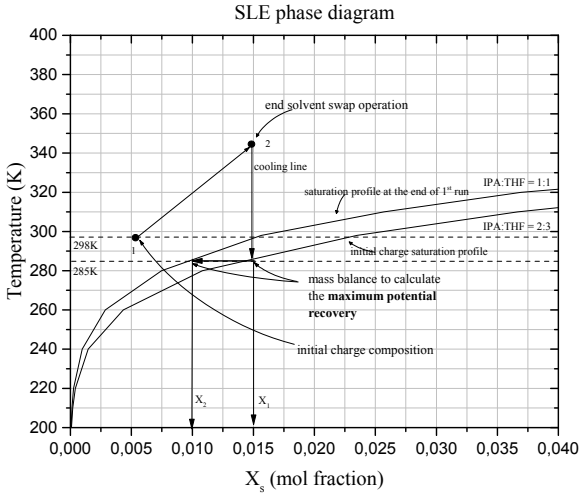


Figure 5.18 Evaluation of the maximum potential product recovery during after the batch distillation. Figure shows the initial composition of the mixture and the corresponding saturation curve (IPA:THF=2:3) and the final composition when the distillation ends together with the corresponding saturation curve (IPA:THF=1:1). Performing the mass balances at the desired crystallization temperature, the potential recovery is evaluated.

To investigate how much swap solvent needs to be charged to obtain a specified product recovery, three operational scenarios are considered. In base case scenario (Scenario 1), there is one swap solvent charge, and in Scenarios 2 and 3 there are two and three swap solvent charges, respectively. Note that Table 5.29 and Figure 5.17 and Figure 5.18 correspond to Scenario 1. The simulation results of the swap operations together with the distillation limits for Scenario 2 and the solid solubility analysis for scenario 2 are shown in Figure 5.19a and Figure 5.19b. After the end of the swap task the obtained mixture (point "2", Figure 5.19) is cooled to ambient temperature and the potential product is calculated to be close to 86%.

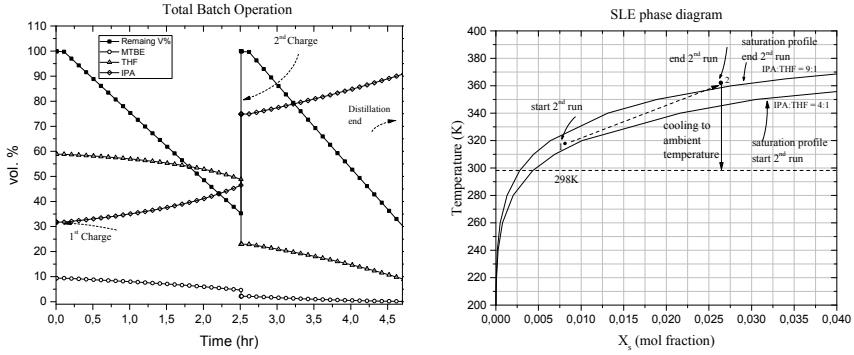


Figure 5.19 Simulation results for Scenario 2, (a) Volumetric composition in the batch still for two swap solvent charges and (b) calculation of the maximum potential product recovery based on the corresponding solid saturation curve.

The simulation results of the batch distillation operation during the second scenario where three swap solvent charges are considered and the corresponding saturation curves are presented in Figure 5.20. Similarly to the analysis before, given the final obtain composition (point "2", Figure 5.20b) and cooling to ambient temperature (point "3", Figure 5.20b), the potential recovery is calculated slightly higher than 89%.

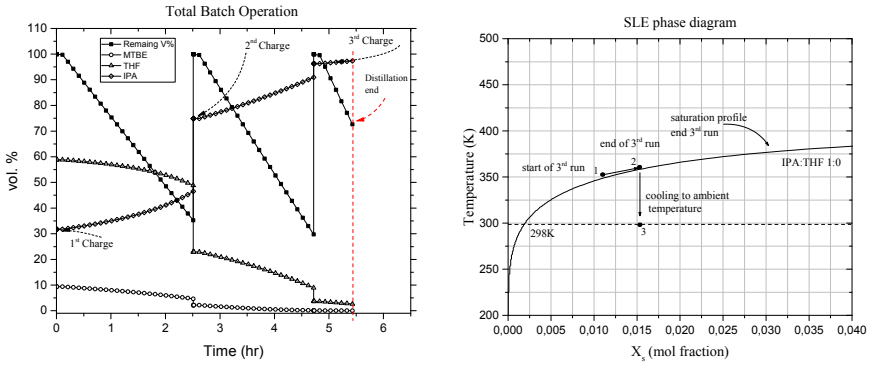


Figure 5.20 Simulation results for Scenario 3, (a) Volumetric composition in the batch still during the second run and (b) calculation of the maximum potential product recovery based on the corresponding solid saturation curve.

The amount of the swap solvent added for every scenario and the calculated potential recoveries are given in Table 5.31. To summarize for the case where 2-propanol is used as a swap solvent, three swap solvent charges are needed to achieve maximum potential recovery by crystallization. The reason for this is that THF is completely removed from the system during the first and the second swap solvent charges. Taking also into account the high solute solubility in THF, lower temperatures are needed in order to recover higher amounts of the solute during crystallization. Therefore, a third swap charge is needed to remove almost the entire original solvent amount and to make the potential product recovery high when crystallization is performed at ambient operating temperatures.

Table 5.31 Scenario description for swap solvent addition and maximum potential product recovery in the crystallization unit.

Scenario	Swap solvent added	Max potential recover, crystallization at 298K
Base case	79 kg	0.00%
Scenario 1	79 kg	85.73%
Scenario 2	79 kg	89.38%

The results of similar analysis performed for the other two selected swap solvents, ethanol and n-butanol, are given as supplementary material (Figure 7.7 and Figure 7.9 and Table 7.12 and Table 7.13 in section B-I.4).The performance criteria are calculated using the simulation results and compared with the results given by Watson et al. [190]. The results are given in Table 5.32 and it can be seen that one of the selected solvents (2-propanol) has also been used by Watson et al. [190], giving similar results with respect to the number of swap solvent charges and the total process yield calculated from experimental data [190]. Considering the performance

criteria and the selected swap solvents using the methodology, the overall process performance is better when n-BuOH is used as swap solvent (see Table 5.32). In case of ethanol, better performance is achieved during the solvent swap task, with respect to the solvent use, solvent losses and operation time, however, lower product recovery and lower overall process yield is achieved in comparison with 2-propanol.

Table 5.32 Summarized results and comparison of results for case study 1.

Solvent swap task	**This study**			**Literature** [190]
Swap solvent	IPA	EtOH	n-BuOH	IPA
Fresh swap charges	3	3	2	3
Swap solvent use (kg)	237	207	148	237
Solvent losses (kg)	350	320	172	n.i.
Distillation operation time (hr)	5.5	5	3.92	n.i.
Crystallization task				
Temperature (K)	298	298	298	298
Max potential recovery (%)	89.38	81.97	91.63	n.i.
Product loss (kg)	0.87	1.47	0.41	n.i.
Total process Yield	70.1%	67%	75%	70-71%

5.2.2 Example B. Heck reaction

Heck reactions with aryl triflates are very common reactions because they are found in a wide range of reaction paths and give access to regioisomeric products [192]. However, due to the lack of commercially available aryl triflates, they need to be produced prior to their use in Heck reactions. Triflates are commonly prepared from phenols and trifluromethanesulfonic anhydride in chlorinated solvents using stoichiometric amounts of amine bases. After the reaction is completed, the salt by-products and the excess of reagents are removed by liquid-liquid extraction. The next reaction step usually needs to be carried out in another solvent, therefore the chlorinated solvent needs to be removed and replaced.

Problem Definition:

a. Selection and evaluation the performance of solvents in solvent swap operation
b. Evaluation of the selected solvents performance for the reaction step

Section A: Reaction pathway identification

Step A.1. Select API or intermediate: **Aryl triflates**

Step A.2. Reaction pathway identification: Searching in reaction type database for aryl triflates reactants utilized via Heck reactions, two reactive pathways were found. The overall reaction path is illustrated in Figure 5.21

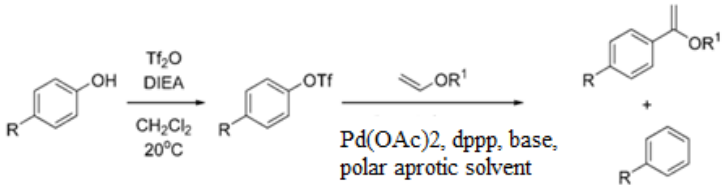


Figure 5.21 Synthesis of the aryl triflate in the first reaction step and utilization in Heck reaction.

Section B: Reaction analysis

In this example, the first reaction step 4-tert-butylphenyl tri-fluoromehtnaesulfonate is the aryl trilfate of interest, which is produced in dichloromenthane (CH_2Cl_2) from 4-tert-butylphenyl alcohol and trifluromethanesulfonic anhydride using Diisopropylethylamine amine donor at 20ºC [192]. In the second step, the product from the first step is combined with alkene coupling partner, amine base, Pd catalyst, and ligand in a polar aprotic solvent at temperature higher than 100ºC. For the second reaction low temperature (below 100ºC) and presence of dichloromenthane (above 5% v/v) decreases dramatically the reaction yield.

After the first reaction step, salt by-products and excess of reagent need to be removed and solvent needs to be replaced with a polar aprotic solvent in order to improve the performance of the second reaction.

Section C: Separation synthesis

The process for the separation of 6-hydroxybuspirone is fixed. Therefore, the steps C.1-C.3, to identify the type and the sequence of unit operations is not necessary to be performed. A simple process diagram with the synthesis of aryl triflates, the liquid-liquid separation by introducing aq. HCl, the solvent swap operation and the second reaction is illustrated in Figure 5.22 [192].

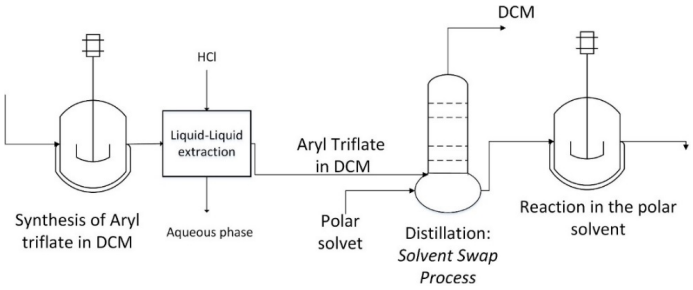


Figure 5.22 Processing task for the case study 2. Reaction in DCM, washing the impurities with aq. HCl, solvent swap, reaction in the swap solvent.

For the selection of the swap solvent, the solvent swap methodology is employed.

Solvent Swap methodology

Step 1. Problem definition: The objective of this example is to remove the original solvent (dichloromethane, DCM) used for the synthesis of aryl triflate and replace it with a polar aprotic organic solvent (swap solvent) for the next processing task which is another reaction (see Figure 5.22).

Step 2.Feasible swap solvents candidates

Dichloromethane has very low boiling point and it can be swapped with almost any solvent that present in the database (Table 4.5) and have a higher boiling point. Using the database (Figure 4.12 and Figure 4.13), a list of feasible swap solvent candidates is identified and given in Table 5.33.

Table 5.33. Feasible swap solvent candidates that can replace DCM. Solvent classification: HBD: hydrogen bond donor, AP: aprotic polar, AALP: aromatic apolar or highly polar, EPD: electron pair donors, AAA: aliphatic aprotic apolar.

Original solvent	Swap solvent candidate	Solvent Swap Process Classification	Vacuum effect	T_b (^oC)	Solvent Classification
DCM	Acetic Acid	Very Easy	No effect	117.9	HBD
	Acetone	Very Difficult	No effect	56.0	AP
	THF	Easy	Negative	65.0	AP
	2-methyl pentane	Very difficult	No effect	60.2	No classification
	Methanol	Easy	No effect	64.8	HBD
	2-propanol	Very easy	Positive	82.3	HBD
	Toluene	**Very easy**	**No effect**	**110.6**	**AP**

Isopropyl Acetate	Very easy	Positive	88.6	No classification
Anisole	Very Easy	Weakly positive	153.7	AALP
Methyl isobutyl ketone	Very Easy	Weakly positive	116.5	No classification
Ethyl Acetate	Very easy	Weakly positive	77.1	AP
2-Methyltetrahydrofuran	Easy	Negative	78.0	No classification
Acetonitrile	Very easy	No effect	81.6	AP
Water	Very easy	No effect	100.0	HBD
N,N-Dimethylformamide	**Very easy**	**Weakly positive**	**152.0**	**AP**
MTBE	Very Difficult	Weakly positive	55.2	EPD
N-Methyl pyrrolidone	Very easy	No effect	202.0	No classification

Step 3. Candidates Analysis

In order to reduce the number of solvents identified in step 2, the swap solvent specifications for the next processing step are taken into account. According to experimental data [192], the swap solvent must be aprotic polar and the reaction usually takes place at temperature higher than 100ºC. Therefore, the solvent must have a high boiling point (>100 ºC) to assure that the solvent remains in the liquid phase during the swap operation [126] and to achieve high product yield [192]. Toluene and DMF are the solvents which satisfy the solvent constrains for the reaction solvent (aprotic solvent and boiling point > 100ºC). The selected solvents (toluene and DMF) are marked in bold in Table 5.33. It should be noted that Hartman et al. [192] also selected these two solvents.

5.2.3 Example C. Synthesis and purification

An API (unknown structure) is produced via hydrogenation reaction in an organic solvent, which can dissolve the reactants and the catalyst, increases the reactivity of the system and it is immiscible with water. After the production of the desired API, the salt impurities are extracted in the aqueous phase and a swap solvent that is suitable for the crystallization replaces the original solvent. For this case study the best performing solvent for the crystallization is toluene [64].

Step 1. Problem Definition

The objective of this example is to identify the solvent that should be used for the reaction task, given that the swap solvent is toluene. The operational tasks needed for this process are shown in Figure 5.23.

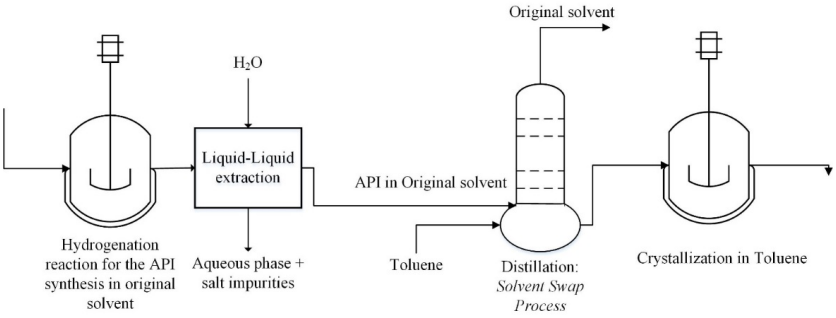


Figure 5.23 Processing tasks for the case study 3. Reaction in an original solvent, followed by washing step, solvent swap to toluene and crystallization in toluene.

Step 2. Feasible solvents candidates

The feasible solvent candidates are identified by looking for solvents that can be swapped by toluene using the swap solvent database (Figure 4.12, Figure 4.13 and Figure 4.14). The list of feasible original solvents are given in Table 5.34.

Table 5.34 The generated feasible original solvents that toluene can swap.

Original Solvent Candidate	Swap solvent	Solvent Swap Process Classification	Vacuum effect
DCM	Toluene	Very Easy	No effect
MTBE		Very Easy	No effect
Acetone		Very Easy	Positive
2-methyl pentane		Very Easy	Positive
Methanol		Conditional	Negative
THF		Very Easy	No effect
EtOAc		Easy	Weakly positive
MeTHF		Very Easy	Weakly positive
MEK		Easy	Weakly positive
MeCN		Conditional	No effect

IPA	Conditional	Positive
IPAc	Very Difficult	Weakly positive
2-methyl-1-propanol	Conditional	Negative
water	Conditional	Weakly negative

Step 3. Candidate Analysis

To reduce the search space, concerns about the reaction step are considered. The solvent needs to have high API solubility and low water solubility. The API structure is not known but some experimental data is available, which shows that the API has very low solubility in toluene and high solubility in 2-methyl-1-propanol (i-BuOH) [64]. Therefore, the solubility parameter of the API should have a value close to 20 $MPa^{½}$<SP<23 $MPa^{½}$ (based on the value of i-BuOH). Considering the solubility parameters and the miscibility in water (retrieved from CAPEC database) the reduced list of the solvents is given in Table 5.35. Note that since the reaction temperature is not known, the boiling point and melting point temperatures are not considered in this analysis.

Table 5.35 The selected original solvents based on the reaction concerns.

Original Solvent Candidate	SolPar ($MPa^{½}$)	Water Solubility
DCM	20.4	Slightly soluble
2-methyl-1-propanol	22.9	Slightly soluble

Based on the analysis and the concerns for the reaction, two solvents are selected: DCM and i-BuOH, where the selection of i-BuOH has also been reported by Hsieh et al. [64].

Step 4. Process validation

Further analysis cannot be performed in this example, as the molecular structure of the API is unknown.

5.2.4 Example D. Ketone intermediate for the LY500307 synthesis

A key intermediate for the production of API LY500307, is produced via the hydrogenation reaction in a solvent mixture of MeOH/EtOAc. After the reaction task has been completed, a swap solvent is added in the mixture to facilitate separation of the product from the reactor through liquid-liquid separation where the organic phase that contains ethyl acetate (EtOAc) and the API while the aqueous phase contains MeOH, water and water soluble impurities. From the organic phase, the original solvent is removed by batch distillation and the product is recovered through a subsequent crystallization task [193].

Step 1. Problem Definition

The objective is to find a solvent that enhances the phase split between methanol and ethyl acetate after the reaction step and the selected solvent should be able to swap the original solvent (ethyl acetate) and should be suitable for the crystallization task.

Step 2. Feasible swap solvents candidates

Using the database (see Figure 4.12 and Figure 4.13), the feasible solvent candidates are given in Table 5.36

Table 5.36 List of generated swap solvents that can replace ethyl acetate.

Original Solvent Candidate	Swap solvent	Solvent Swap Process Classification	Vacuum effect	SolPar ($MPa^{½}$)
EtOAc	Acetic Acid	Easy	Weakly Positive	19
	2-propanol	Conditional	Positive	23.4
	Toluene	Easy	Weakly Positive	18.3
	Anisole	Very easy	Weakly Positive	20.1
	MIBK	Easy	Weakly Negative	17.4
	NMP	Easy	No effect	23.2
	Water	Conditional	No effect	47.8
	DMF	Very easy	Weakly Positive	23.9
	Ethanol	Difficult	Positive	26.1
	1-butanol	Very easy	Weakly Positive	23.3
	2-methyl-1-propanol	Very easy	No effect	22.9

Step 3. Candidates Analysis

The swap solvent needs to dissolve the API and it should not be miscible with a mixture of MeOH/water. Using ICAS-ProPred the solubility parameter of the API is calculated, SolPar = 20.61 $MPa^{½}$. Therefore, solvents that have solubility parameter values between 19 $MPa^{½} \leq$ SolPar $\leq$ 21 $MPa^{½}$, are good candidates the selected solvents are given in Table 5.37. Based on the analysis, four possible swap solvents are identified. These solvents can be further analyzed for their performance in the liquid-liquid separation task and the crystallization task by performing LLE and SLE calculations, respectively. The use of toluene as the swap solvent has also been reported by Johnson et al. [193].

Table 5.37 The selected solvents for the case study 4.

Original Solvent Candidate	Swap solvent	SolPar^{½}
EtOAc	Acetic Acid	19
	Toluene	18.3
	Anisole	20.1
	MIBK	17.4

Based on the methodology four solvents have been selected as swap solvent, acetic acid, toluene (selected in the literature, Johnson et al., [193]), anisole and MIBK.

Step 4. Process validation

Further analysis was not performed in this example.

5.2.5 Conclusions

The methodology has been applied to several case studies where it has been shown that it is possible to identify solvents that have higher potential for specific solvent swap tasks. The swap solvent selections are validated through dynamic simulations with rigorous models different use of solvents, operations and operation modes. One aspect not studied but could be interesting is to see how swapping of solvents could be avoided, for example, selecting the same solvents for more than one processing step or completely avoid the use of solvents.

5.3 Case study 3: Production of L-2 Aminobutyric acid-Process intensification

L-aminobutyric acid is an unnatural amino acid that it serves an intermediate for the synthesis of key chiral APIs such as Levetiracetam (anti-epileptic), Ethanmbutol (anti-tuberculotic) and Brivaracetam (anti-tuberculotic) [194].

5.3.1 Problem definition

Objectives:

- Investigation of the effect of solvent in reactionperformance.
- Investigation of the advantages of process intensification and continuous operation
- Process development

5.3.2 Section A. Reaction pathway identification

Step A.1. Select API or intermediate: L-2-aminobutyric acid

Step A.2. Reaction pathway identification: Using the reaction database, several chemocatalytic and biocatalytic reactions have been suggested for the synthesis of unnatural amino acids.

The selected reaction pathway is illustrated in Figure 5.24,

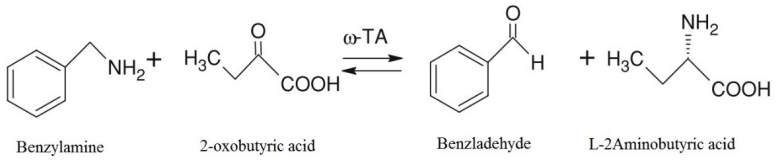


Figure 5.24 The reaction pathway as it has been identified from the reaction type database.

5.3.3 Section B. Reaction analysis

The reaction takes places in the aqueous phase at mild conditions. 2-oxybutyric acid (OA) reacts with benzylamine (BA) which acts as amine donor to produce benzaldehyde (BD) and L-2-aminobutyric acid (AABA). The reaction is equilibrium controlled and catalysed using ω-transamination (ω-TA) from *Vibrio fluvialis*. It exhibits amine donor inhibition when the concentration of benzylamine is above 100mM and it has shown severe product inhibition by benzaldehyde. To overcome the equilibrium limitations, the introduction of an organic solvent in the reaction mixture to create a second liquid phase and extract the inhibitory product has been used to increase the reaction rate and shift the equilibrium towards the product site (96% in biphasic system compared to 39% of the single phase system), with very high enantiomeric selectivity (ee%>99%) [151]. The reaction is a slow reaction (Type C) and it is operated in batch mode. However, according to the unit operation database, for this kind of operation, enzymatic reaction in two phase system with product removal, continuous operation might be beneficial for the system. Using the unit operation database, an enzyme multiphase continuous reactor is proposed (EMR) which has the advantage of completely separating the enzyme with the organic phase to avoid any potential contact of the enzyme with the organic phase.

The summary of the reaction analysis step is given in Table 5.38.

Table 5.38 Reaction analysis for the oxidation of buspirone to 6-hydroxybuspirone.

Reaction Step: Oxidation of buspirone		
Step B.1 Data collection	Reactants:	2-Oxybtyric acid (OA); Benzylamine (BA)
	Main Product	L-Aminobutyric acid (LA)
	Side Products	Benzaldehyde (BD)
	Phases	Single (L) or Biphasic (L-L)
	Solvent	Water or Water/Organic
	Solvent Role	Water: Reaction medium Organic: Create another phase to extract the by-product
	Catalyst	ω-Transamase
	Reaction conditions	37°C; 1 atm
	Reaction data	C= 39% (or 96%) ee(%) > 99%
	Experimental data	Conversion vs. time
	Scale	mg scale (reaction volume ml scale)
	Kinetic Model	Available
Step B.2 Kinetic Study	Reaction Class	Type C
	Mass Transfer	Mass Transfer Limitation
	Heat Transfer	No information
	Equilibrium	Yes
	Control Mechanism	Equilibrium controlled
	Kinetic model	Fitted (see Figure 5.25)
Step B.3 Process evaluation	Temperature	37°C (higher temperature results in higher enzyme deactivation, lower temperature results in very low reaction rates)
	Mixing	Gentle mixing
	Concentration	C_{BA}<100 mM
	Stoichiometry	1:1.4
	Pressure	1 atm
	pH	7
	Solvent	Table 5.40
	Process conditions	37°C; 1 atm, t =5hr
	Process performance	C: 91%; ee: >99%
Step B.4 Batch or continuous	Potential benefits	Enzyme deactivation Lower amount of mass utilized Solvent recycle
	Unit operation database	Enzyme multiphase membrane reactor
	Decision	Batch, Section 5.3.3.2
Step B.5 Reactor design		Not performed
Step B.6 Separation Objectives		Separation of the phases Recover organic solvent Purify main product

The kinetic model has been developed using the multiphase reaction modelling framework by Anantpinijwatna et al. [173]. Available experimental data [151] used for parameter estimation. The modelling fitting [25], [195] is illustrated in Figure 5.25.

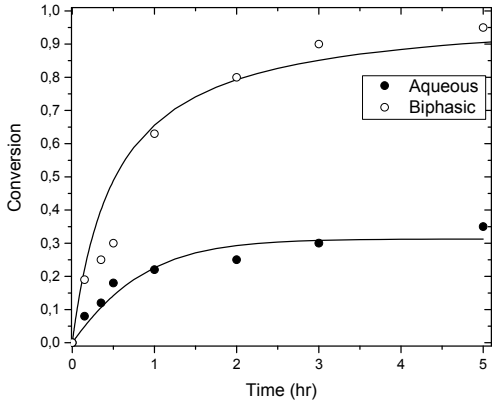


Figure 5.25 Comparison between model prediction for biphasic and single phase: solid line) and experimental data (biphasic: open circles and single phase: Filled circles). Organic solvent: Hexane.

5.3.3.1 Solvent selection for step B.3

To create a second phase, the organic solvent should be selected that is immiscible with the aqueous phase and it selectively dissolves the inhibitory product. For the solvent selection the partition coefficient of the compounds involved in reaction are analysed and given in Table 5.39. The partition coefficient of the compounds that are desired to remain in aqueous phase should be high, the compounds with low partition coefficients migrate in organic phase [195].

Table 5.39 Partition coefficient of the involved species in the long chain hydrocarbon solvents [25].

Partition $\left(\frac{\gamma_i^{org}}{\gamma_i^{aq}}\right)$	**Benzylamine**	**2OA**	**AABA**	**Benzaldehyde**
Hexane	1.014	1.20×10^{5}	2.22×10^{5}	1.24×10^{-4}
Heptane	0.849	1.85×10^{5}	2.81×10^{5}	1.20×10^{-4}
Isooctane	0.323	1.20×10^{5}	1.46×10^{5}	6.29×10^{-5}
Octane	0.338	2.68×10^{3}	8.40×10^{3}	7.69×10^{-5}

The evaluation of the reaction performance in terms of half-time, overall reaction rate, conversion and obtained product for the considered solvent is given in Table 5.40. Maximum conversion and reaction rates are achieved using isooctane and octane as solvent. However, the productivity of the system using octane and isooctane is lower compared to the productivity achieved when hexane or heptane is used [195]**.**

Table 5.40 Predicted reaction information carried out in different solvents [195].

Solvents	**Half-Life (hr.)**	**Overall Reaction Rate (µmol·h-1)**	**Maximum Conversion**	**Maximum Product (µmol)**
Hexane	0.425	0.980	0.950	46.075
Heptane	0.475	0.977	0.947	45.930
Isooctane	0.302	1.380	0.970	33.950
Octane	0.311	1.340	0.970	33.950

Considering the results given in Table 5.40, selecting a solvent depends on the objectives of the study. Selecting, for example, octane as the extraction solvent, the product losses are high but at the same time, the separation of the phase containing the product might be less complicated. However, for the production of pharmaceutical product, the most important criterion is the product recovery. Therefore, here, hexane is used as the extraction solvent.

5.3.3.2 Step B.4 Batch or continuous?

According to unit operation database, the batch reactor can be converted into continuous enzyme multiphase reactor. In this section an evaluation between the two operation modes is performed.

5.3.3.2.1 Comparison of the batch and the continuous reactive system.

Here, the objective is to compare the batch operation and the proposed continuous operation (EMR). It is should be noted that the membrane which selectively separates the inhibitory product from the reaction mixture, to our knowledge, does not exist. However, the purpose here is to examine whether a continuous operation of the particular system is beneficial or not. In case, that process improvements can be achieved by converting, the batch process to continuous, further experimental verification is needed. Table 5.41 gives the description of the two scenarios of interest, the production target, the operation time, initial concentration, and required volume for the aqueous and organic phase.

Table 5.41 Scenario of interest for the synthesis of L-2-aminobutyric acid.

Scenario	**1**	**2***
Reactor	Batch	EMR
Productivity	43 mmol	8.64 mmol/hr
Operation time, hr	5	5
Concentration, mM	50	70
Aqueous phase volume, ml	1	0.17
Organic phase volume	5 x V_{aq}	5 x V_{aq}

*For the second scenario, an EMR reactor model has been developed based on the reaction model. The total reactor model; functional description (Figure 7.10), model construction (Table 7.17 and Table 7.18), model analysis (Table 7.19)is given in Appendix C.

The simulation results are given in Table 5.42, where the productivity per reaction volume has been calculated and compared. The use of continuous multiphase enzyme membrane reaction has demonstrated much higher productivity per reactor volume than the batch operation.

Table 5.42 Reaction productivity for the batch system.

Scenario	Conversion %	Ammount, mmol	Productivity mmol/ reactor volume
1	91%	43.2 mmol	7.2
2	91.6%	43 mmol	38

5.3.3.2.2 Simulation Results

The developed model now is used to investigate the production at higher production rate (92mmol/hr, approximately 10 times higher than the productivity rate previously used in Section 5.3.3.2). The reaction conditions are given in Table 7.21 (Appendix C) where for all the variables identified from the degree of freedom analysis a value has been assigned. The results are illustrated in Figure 5.26, where in Figure 5.26a, the concentration of the reaction species in the aqueous phase is illustrated. The concentration of the inhibitory product (BD), as it was expected, has very low value, close to zero, which means that is efficiently separated in the organic phase (see Figure 5.26b). In Figure 5.26a, it can be seen that the concentration of the benzylamine during the reaction is not approaching the concentration limit (100 mM) where the BA starts to inhibit the enzyme. Finally, the conversion of the main substrate is illustrated in Figure 5.26c.

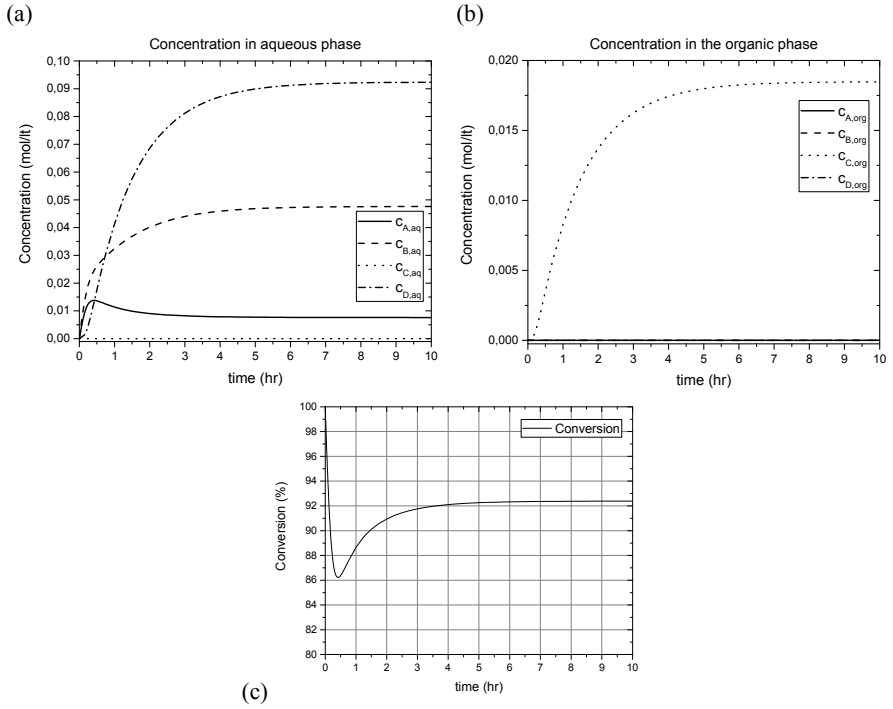


Figure 5.26 Simualtion results of the EMR reactor, where A: OA, B: BA, C: BD and D: AABA. (a) concentration in aquesous phase, (b) concentration in organic phase, (c) conversion.

5.3.4 Section C. Separation synthesis

Steps C.1-C.2: The alternatives for the separation process of L-2-aminobutyric acid has been generated using step C.1-C3. The pure compound properties for the compounds involved in the process are given in Table 7.24 (Appendix C). The pure compound properties used to generate the binary ratio matrix, to identify the separation tasks and generate separation alternatives.

Step C.3. Separation process selection

The generated list of the selected process alternatives to separate the organic phase with the by-product and to recover the product from the aqueous phase are listed in Table 5.43.

Table 5.43 Separation process alternatives for production of 2-Laminobutyric acid A: water, B: BA ,C: 2OA, D: AABA, E: BD, F: Hexane.

Rank	Process alternatives [SFILES]
1	(rABCDEF)(spABCD/EF)(lmE/F)[[(oE)]1(pF)](crD/ABC)[(oD)](dsAB/C)[(oAB)](oC)
2	(rABCDEF)(spABCD/EF)(lmE/F)[[(oE)]1(pF)](crCD/AB)[(oAB)](scSC/D)[(oD)](scS/C)[2(oS)](oC)
3	(rABCDEF)(spABCD/EF)(lmE/F)[[(oE)]1(pF)](scD/SABC)[(oD)](dsS/ABC)[(oS)](oABC)
4	(rABCDEF)(spABCD/EF)(lmE/F)[[(oE)]1(pF)](dsAB/CD)[(oAB)](scSC/D)[(oD)](dsS/C)[2(oS)](oC)

5.3.5 Section D. Process Simulation/Evaluation

From section C, two state task networks (Figure 5.27) have chosen for further evaluation.

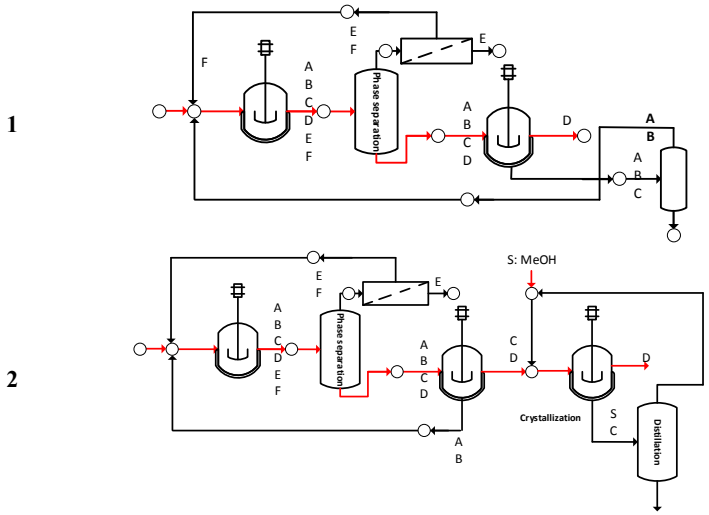


Figure 5.27 The two selected state task networks where A: water, B: BA ,C: 2OA, D: AABA, E: BD, F: Hexane.

Step D.1 Process simulation/evaluation

Mass and energy balances calculation were performed for both cases using Hexane as the extraction solvent. Then, the state task network 1 is compared using two different extraction solvents, hexane and octane. The results of the simulation are given in Table 5.44, where it can be seen that the state task network 1 required much less energy than the state task network 2 and it generates 6% less waste per kg of product. Comparing now the state-task network 1 using two different solvents, hexane and octane, it can be seen that the energy requirements are lower and the generated waste per kg of product using octane is higher than using hexane. These results verify the conclusions that made after the extraction solvent selection step where it was concluded that the product recovery is enhance when hexane is used, however the waste generation increases by 3% as bigger amounts of compounds involved in the reaction are extracted in the organic phase when octane is used.

Table 5.44 Batch process performance of the process to produce 2-L-aminobutyric acid. State-task network 1 and 2 compared using hexane as extraction solvent and state-task network 1 compared for two diffrent extraction solvents.

Performance criteria	**Extraction solvent**		
	Hexane		**Octane**
	State-task network	State-task network 2	State-task network 1
Energy Requirements MJ/kg product	0.93	+ 272%	-8.53%
Waste kg/kg product	1.26	+6%	3.17%

Environmental impact analysis using the WAR algorithm in ICAS was performed for the state-task network 1 and 2 using hexane as solvent. Figure 5.28, illustrates the results where it can be seen that this process contributes to ATP category where in the rest of the categories the impact is negative that is a positive for environmental point of view. It is expected that when octane is used as solvent, the environmental impact is going to be higher due to the increased waste generation. Nevertheless, octane is not selected for further analysis due to high product losses and not significant process improvements.

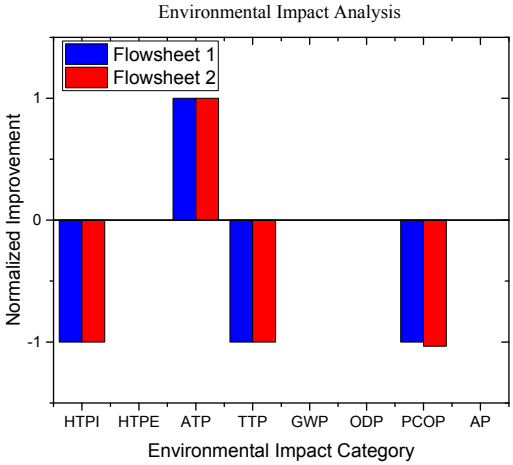


Figure 5.28 Normalized comparison of the enironmental impact of the process to produce L-2-aminobutyric acid for two different state task networks. HTPI: human toxicity potential by ingestion, HTPE: human toxicity potential by exposure, ATP: aquatic toxicity potential, TTP: terrestial toxicity potential, GWP: global warming, ODP: ozone depletion potential, PCOP: Photochemical oxidation potential and AP: acidification potential.

5.3.6 Conclusions

In this case study, a multiphase reactive system selected to demonstrate the use of a solvent to achieve reaction improvement in terms of performance. Here, the role of the solvent is to extract the inhibitory product (in this case the by-product) and shift the equilibrium towards the product side. In this study a kinetic model develop and evaluation of the different solvents was performed by Anantpinijwtna [195]. Based on the kinetic model, a continuous multiphase enzymatic membrane reactor model developed and compared with the batch reactor model showing higher productivity per reaction volume. Finally, process alternatives to separate the reaction mixture have been generated and evaluated through simulations. An experimental verification of this new design is needed.

5.4 Case study 4: Glucose isomerization

Glucose isomerization is an important processing step for the food industry as the high fructose syrup (HFS) product it produces, is widely used for its ability to improve the sweetening and color of food products, is metabolized without the intervention of insulin and is absorbed slower than glucose. The GI-plant to produce high fructose syrup usually consists of a pre-treatment part, a reaction part where glucose is converted to fructose and a separation part where fructose is separated and recovered and the unreacted glucose is recycled back. The reaction is an equilibrium controlled enzyme reaction and it is usually carried out in fixed bed reactors where the enzyme is immobilized. Due to enzyme deactivation the reactors in typical GI plants are operated in parallel to keep a consistent reactor effluent.

5.4.1 Problem definition

The objective of this case study is to first develop and then use a multi-scale model that can accurately describe the behaviour of an industrial glucose isomerization reactor so that it can be used after validation, for the simulation-based analysis to identify efficient operational modes of a GI plant. In particular, the model must consider different phenomena that occur in the reacting system such as the reaction kinetics, the substrate diffusivity and the enzyme decay as a function of the temperature.

5.4.2 Section A: Reaction pathway identification

For the glucose isomerization process, the reaction scheme is known, glucose together with the free enzyme react to form the complex enzyme and then the product is released, and the reaction is an equilibrium-limited reaction. The reversible glucose-fructose enzymatic isomerization is given by the following expression:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SE \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} P + E \tag{1}$$

Where S is the substrate (glucose), E is the free enzyme; SE the complex enzyme formed during the reaction and P the product (fructose).

5.4.3 Section B: Reaction analysis

The glucose isomerization reaction is catalyzed by isomerase, the reaction temperature is around 55-60^{o}C and the feed concentration 45-50% w/w glucose. The reactors in the plant are fixed bed reactors operated in a semi-continuous mode which means that the reactor runs for certain period of time, when the enzyme is completely inactivated the operation stops and the operation restarts, when new enzyme is loaded in the reactor. During the operation, the reaction conversion is decreasing due to the enzyme inactivation. However, it is preferred to maintain the conversion constant and it can be achieved by reducing the substrate flowrate throughout the duration of the operation.

5.4.3.1 Reactor Modelling

Step I.1: Modelling objective

Glucose isomerization to fructose is the process of interest and more specifically, a reactor plant where high fructose syrup (HFS) is produced by glucose isomerization using isomerase as the enzyme is to be studied. The objective here is to develop a multi-scale reactor model that

describes the reaction kinetics, the enzyme decay and the internal diffusivity of the substrate as function of temperature. Model analysis, model identification, model evaluation and validation are to be performed. The validated model is to be used for simulation of a typical glucose isomerization reactor to identify operational modes that maximize the productivity.

Step I.2. System information and documentation

Step I.2.1: Functional description/sketch of the system to be modelled.

For this process the reaction scheme is given in equation(1), glucose together with the free enzyme react to form a complex enzyme and then the product is released. The reaction is an equilibrium-limited reaction. A typical GI reactor plant is illustrated in Figure 5.27. The reactor plant consists of NR (= 10-20) fixed-bed reactors, where the enzyme is immobilized in the reactor. The reaction is an equilibrium reaction where fructose is obtained as a product and the reaction takes place in the enzyme pellets where the glucose is diffused. The enzyme activity decreases during the operation due to enzyme inactivation. The output from reactor is desired to be consistent and operated at values of glucose conversion between 42-45%. To keep the conversion constant, the inlet flowrate is adjusted (decreased) as the enzyme activity decreases during the operation. The reaction usually takes place between 55-60 ^{o}C. Lower temperatures are usually avoided due to the risk of microbial contamination of the substrate and higher temperatures are usually avoided due to faster enzyme inactivation (Novozymes A/S).

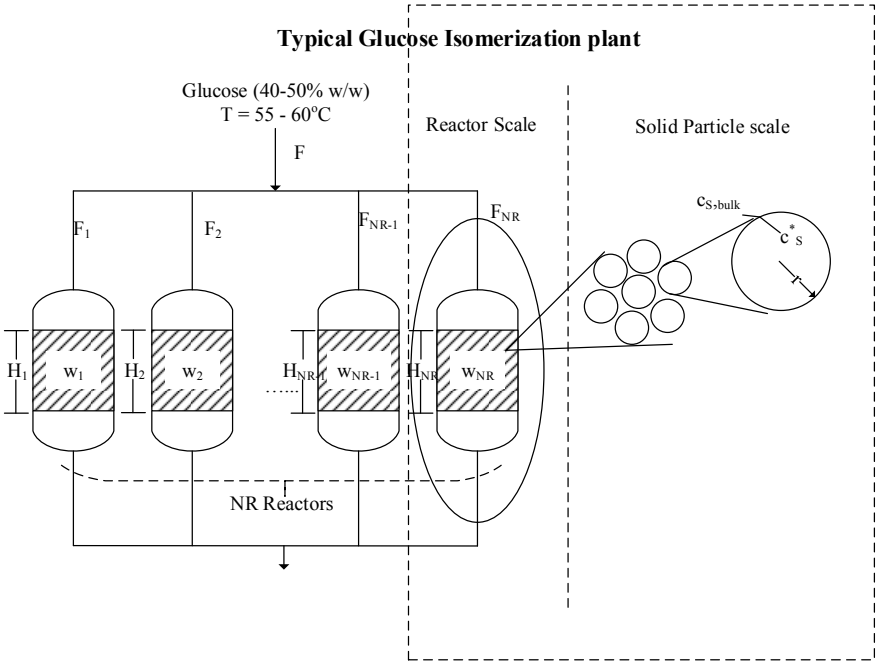


Figure 5.29 A typical glucose isomerization (IG) reactor plant with N fixed bed reactors. The operating temperature is between 55^{o}C-60^{o}C, the dry substance content is between 45-52% w/w and it depends on the operation temperature (the lower the temperature the higher the dry solids).

Step I.2.2: Phenomena in the system.

The following phenomena are identified in the reactor system:

- Enzymatic equilibrium reaction.
- Enzyme decay.
- Substrate diffusion in the enzymatic pellets.
- Mass transfer between the substrate's flows to the interface of the pellets.
- Flow in fixed-bed reactor.

Step I.2.3: Modelling information

For the development of the reactor model, the phenomena described in Step I.2.2 have to be mathematically described and combined with other classes of model equations. The reaction kinetics, the reactor modelling, and the enzyme decay for different enzymes have been described in the literature (see Table 5.45).

Table 5.45 Review of the GI modelling studies.

Authors	Glucose Isomerase	Model types	Available data
[196]*	Streptomyces sp.	• Reaction kinetics • Batch reactor model • Enzyme decay	a. Kinetic parameters estimation using experimental data from Takasaki et al., 1969 b. Enzyme Inactivation parameters
[197]	Streptomyces sp.	• Reaction Kinetics • Reactor Model o Including enzyme decay Enzyme decay	Michaelis-Menden parameter estimation from initial reaction rate experiments
[198]	Bacillus sp.	• Reaction Kinetics	Michaelis-Menden parameter estimation from initial reaction rate experiments
[199]	n.i.	• Diffusion resistance • Enzyme decay	Investigation of enzyme decay upon diffusion limitations and different decay rates for reactions with Michaelis-Menden mechanism
[200]	n.i.	• Reaction Kinetics • Reactor Model o Including enzyme decay	Investigation of reaction conditions (T, pH, operation cost, particle size)
[201] [202]	Swetase	• Reaction Kinetics • Reactor Model o Including enzyme decay Enyzme decay	Michaelis-Menden parameter estimation from initial reaction rate experiments Enzyme inactivation kinetics
[203]	n.i.	• Reactor model • Internal Diffusion	Dynamic model for fluidized-bed reactor

[204]; [205], [206]	Sweetzyme T	• Reaction Kinetics • Reactor Model o Including enzyme decay Enzyme decay	Michaelis-Menden parameter estimation from rom initial reaction rate experiments Enzyme inactivation kinetics
[207]; [207];[208]; [209]	Sweetzyme IT	• Reaction Kinetics • Reactor Model	Michaelis-Menden parameter estimation from initial reaction rate experiments Fixed bed reactor modelling without including enzyme decay and assuming reaction at the interface of the enzyme pellet Kinetics of a Three-Step Isomerization of Glucose to Fructose
[210]	Sweetzyme IT	• Reaction Kinetics • Reactor Model	Michaelis-Menden parameter estimation from initial reaction rate experiments Simulated moving bed reactor modelling

The earlier studies have mainly aimed at process improvements by evaluating the reaction kinetics, enzyme inactivation and the effect of process variables such as the inlet flowrate, the temperature and the inlet glucose concentration. The objective in this project, however, is to combine all these effects in one multi-scale mathematical model that can describe the important phenomena related to increased product yield and design-analysis of an industrial GI plant.

Step I.2.4: Assumptions:

Reaction Kinetics:

- By-products are formed in minor amounts so their formation can be neglected.
- Briggs-Haldane approach is considered for the enzyme kinetics where the enzyme complex concentration is assumed to rapidly approach a steady state and after the initial phase its concentration will remain constant ($\frac{d[SE]}{dt} = 0$).

Fixed-bed reactor model:

- Superficial velocity is high enough so that the external mass transfer resistance is not dependent on velocity.
- Axial dispersion is considered. It has been shown that the effect of the axial dispersion is negligible when convection is higher than diffusion; high values of Peclet number [211]. In this model, the effect of axial dispersion is considered to make sure that it is taken into account when Peclet number is lower close to the end of the operation.

- The radial dispersion is neglected. It has been shown that for a small ratio of column diameter to column length and large values of fluid velocity the radial dispersion can be neglected [212], [213].

Particle diffusion model:

- Enzyme is inside the catalytic pellets and there is no partitioning of the enzyme between the solid and the liquid. Therefore, the substrate is diffused inside the catalytic pellet where the reaction takes place.
- The enzyme is uniformly immobilized in the pellet. Therefore, the enzyme deactivation through the particle is the same during the operation.
- The enthalpy of the reaction is very low so no temperature gradient within the pellet.

Enzyme decay

- The enzyme decay follows first order inactivation

Step I.2.5: System data.

Experimental data is available from Novozymes A/S. Measure data for enzyme activity for the Sweetzyme T enzyme was measured, as a function of the time for a temperature range (55 ^{o}C-90 ^{o}C) is available.

5.4.3.2 Phase II. Model construction

Step II.2: Model development

The developed multi-scale reactor model consists of balance equations (Partial Differential Equations, PDEs) and constitutive equations (Algebraic Equations, AEs) and it describes the diffusion of the substrate in the enzyme, the reaction and the enzyme decay that are taking place in one scale (the enzymatic pellet) and the flow in the fixed bed reactor that is the second scale. The model equations are listed in Table 5.46-Table 5.48 and Table 5.50, and they are described in more detail in Appendix D. Table 5.46 gives the balance equations, the Eq. (2) describes the dimensionless concentration distribution of the substrate as function of the dimensionless reactor length with respect to time subject to the boundary and the initial conditions. The balance Eq. (3) in Table 5.46, describes the diffusion of the substrate in the enzymatic pellet and the reaction as a function of the dimensionless pellet radius and the dimensionless time subject to the boundaries and initial conditions.

Table 5.46 Mass balance equations for GI reactor model. Partial differential equations (PDEs).

Description	Equation	Equation Number	Number of Equations
Balance Equations			
Fixed bed reactor	$\frac{\partial y_s}{\partial \tau} = \frac{1}{Pe}\frac{\partial^2 y_s}{\partial \xi^2} - \frac{\partial y_s}{\partial \xi} - a\left(y_s - y_s^*\right)$	(2)	1
Two independent variables (1. dimensionless time: τ and 2. Dimensionless length z)			
Discretised variable: ξ (dimensionless reactor length), ODE solution with respect to τ			
Solution method: method of lines (number of points: 10)			
Subject to:	$IC: y_s = 0 \ for \ \tau = 0, \xi \geq 0$		
	$BC1: -\frac{1}{Pe}\frac{\partial y_s}{\partial \xi} + y_s = 1, \ for \ \ \tau > 0, \xi = 0$		
	$BC2: \frac{\partial y_s}{\partial \xi} = 0, \ for \ \ \tau > 0, \xi = 1$		
Diffusion in catalyst pellet	$\frac{\partial y_s^*}{\partial \tau} = Q_2\left(\frac{\partial^2 y_s^*}{\partial \lambda^2} + \frac{2}{\lambda}\frac{\partial y_s^*}{\partial \lambda}\right) - Q_1 y_E \frac{y_s^* - y_{s,eq}}{1 + \left(y_s - y_{s,eq}\right)Q_3}$	(3)	1
Subject to:	$IC: y_s^* = 0 \ for \ \tau = 0, \lambda \geq 0$		
	$BC1: \left.\frac{dy_s^*}{d\lambda}\right\|_{\lambda=0} = 0, \ for \ \ \tau > 0, \lambda = 0$		
	$BC2: y_s^*\big\|_{\lambda=1} = y_{S,bulk} \ \ for \ \ \tau > 0, \lambda = 1$		
Two independent variables (1. dimensionless time: τ and 2. Dimensionless length z)			
Discretised variable: λ (dimensionless reactor length), ODE solution with respect to τ			
Solution method: method of lines (number of points: 10)			
Total number of PDEs			**2**

The enzyme decay equations are given in Table 5.47,

Table 5.47 Enzyme decay for GI reactor model.

Description	Equation	Equation Number	Number of Equations
Enzyme decay	$\frac{dy_E}{d\tau} = -k_a y_E$	(4)	1
Subject to:	$IC: y_E = 1, \tau = 0$		
Total Number of ODEs			**1**

The partial differential equations (PDEs) have been converted to initial value problem (IVP) by discretizing them using the method of lines with respect to the reactor length and the particle radius respectively. Table 5.48 gives the balance equation describing the flow in the reactor and the balance equation describing the diffusion in the enzymatic pellet after the discretization. The discretization performed using the method of lines and considering 10 discretization points.

Table 5.48 Discretized partial differential equations for GI reactor model using the method of lines and converted to initial value problem.

Description	Equation	Equation Number	Number of Equations
Balance Equations			
Fixed bed reactor	$\frac{\partial y_{s,n}}{\partial \tau} = \frac{1}{Pe}\frac{y_{s,n+1} - y_{s,n} + y_{s,n-1}}{\Delta\xi^2} - \frac{y_{s,n+1} - y_{s,n-1}}{2\Delta\xi} - \alpha\left(y_{s,n} - y_{s,0}^{*}\right)$	(5)	10
Subject to:	$IC: y_{s,n} = 0 \; for \; \tau = 0, \xi \geq 0$		
	$BC1: -\frac{1}{Pe}\frac{y_{s,2} - y_{s,0}}{2\Delta\xi} + y_{s,0} = 1, \; for \; \tau > 0, \xi = 0$		
	$BC2: \frac{y_{s,10} - y_{s,8}}{2\Delta\xi} = 0, \; for \; \tau > 0, \xi = 1$		
Diffusion in catalyst pellet	$\frac{\partial y_{s,n}^{*}}{\partial \tau} = Q_2\left(\frac{y_{s,n+1}^{*} - y_{s,n}^{*} + y_{s,n-1}^{*}}{\Delta\lambda^2} + \frac{2}{\lambda}\frac{y_{s,n+1}^{*} - y_{s,n-1}^{*}}{2\Delta\lambda}\right) - Q_1 y_E \frac{y_{s,n}^{*} - y_{s,eq}}{1 + \left(y_{s,n}^{*} - y_{s,eq}\right)}$	(6)	10
Subject to:	$IC: y_{s,n}^{*} = 0 \; for \; \tau = 0, \lambda \geq 0$		
	$BC1: \frac{y_{s,2}^{*} - y_{s,0}^{*}}{2\Delta\lambda} = 0, \; for \; \tau > 0, \lambda = 0$		
	$BC2: y_{s,10}^{*} = y_{S,bulk} \; for \; \tau > 0, \lambda = 1$		
Total number equations			**20**

Now, the problem has been converted to IVP and the total number of ordinary differential equations including the enzyme decay is 21, so the initial conditions, which are required, are 21. Table 5.49 gives the dependent variables, the number of the dependent variables, the initial conditions needed and their initial values.

Table 5.49 Initial values for the dependent variables for GI reactor model.

Dependent variable	*Number of variables*	*Initial conditions*	*Initial Value*
$\mathbf{y_s}$	10	10	0
$\mathbf{y_s^*}$	10	10	0
$\mathbf{y_E}$	1	1	1

The constitutive equations needed for the solution of the balance equations are given in Table 5.50.

Table 5.50 Constitutive equations for GI reactor model.

Description	Equation	*Equation Number*	Number of Equations
Temperature in K	$T = 273.15 + \theta$	(7)	1
Arrhenius Expression, k_j	$k_j = A_j \exp\left[-\frac{E_j}{RT}\right]$	(8)	5 (j: v_{mf}, v_{mr}, k_{mf}, k_{mr},d)

Equilibrium constant, K_{eq}	$K_{eq} = \frac{k_{v_{mf}} k_{k_{mr}}}{k_{v_{mr}} k_{k_{mf}}}$	(9)	1
Equilibrium conversion, X_{eq}	$X_{eq} = \frac{K_{eq}}{1 + K_{eq}}$	(10)	1
Equilibrium dimensionless concentration, y_{eq}	$y_{eq} = y_{s,}\big\|_{t=0} \left(1 - \frac{X_{eq}}{100}\right)$	(11)	1
Maximum apparent reaction rate, V_m	$V_m = \left[1 + \frac{1}{K_{eq}}\right] \frac{k_{k_{mr}} k_{v_{mf}}}{k_{k_{mr}} - k_{k_{mf}}}$	(12)	1
Apparent Michaelis-Menden constant, K_m	$K_m = \left[1 + \left(\frac{1}{k_{mf}} + \frac{K_{eq}}{k_{mr}}\right) y_{eq} c_{S,0}\right] \frac{k_{mr} k_{mf}}{k_{mr} - k_{mf}}$	(13)	1
Cross Section, A	$A = \frac{\pi}{4} d_b^2$	(14)	1
Superficial Velocity, U_0	$U_0 = \frac{F_0}{A\,\varepsilon}$	(15)	1
Particle Reynolds Number, Re_p	$\mathrm{Re}_p = \frac{\rho\, d_p U_0}{\mu}$	(16)	1
Schmidt Number, Sc	$Sc = \frac{\mu}{\rho D_m}$	(17)	1
Dispersion Diffusivity, D_L	$D_L = D_m \left[0.65 + 0.5\left(\mathrm{Re}\, Sm\right)^{1.2}\right]$	(18)	1
Reaction Rate, R_s	$R_s = -\frac{1}{w\, c_{S,0}} \frac{dy_S^*}{dt} = -\frac{V_m \left(y_S^* - y_{eq}\right)[S]_0}{K_m + \left(y_S^* - y_{eq}\right)[S]_0}$	(19)	1
Peclet Number, Pe	$Pe = \frac{H U_0}{D_L}$	(20)	1
Dimensionless variable, Q_4	$Q_4 = \rho_{cat} \frac{V_m}{K_m}$	(21)	1
Dimensionless variable, Q_1	$Q_1 = \frac{Q_4 H \varepsilon}{U_0}$	(22)	1
Effective Diffusivity correlation	$D_s = 7.6032 x 10^{-6} \left\{\frac{24000}{R}\left(\frac{1}{T} - \frac{1}{333}\right)\right\}$	(23)	1
Thiele Modulus, φ	$\varphi = \frac{R_p}{3}\sqrt{\frac{Q_4}{D_s}}$	(24)	1
Dimensionless variable Q_2	$Q_2 = \frac{H D_s \varepsilon}{U_0 R_p^{\,2}}$	(25)	1
Dimensionless variable Q_3	$Q_3 = \frac{[S]_0}{K_m}$	(26)	1
Mass transfer Wilson-Geankoplis correlation, k_L	$k_L = 1.09 \frac{U_0}{\varepsilon} \mathrm{Re}^{-2/3}\, Sc^{-2/3}$	(27)	1

Dimensionless mass transfer, α	$\alpha = \frac{R_p}{3} k_L \frac{H}{U_0}$	(28)	1
Substrate conversion, X	$X = \frac{[S]_0 - y_S\|_{\xi=1} \cdot [S]_0}{[S]_0} x100\%$	(29)	1
Correction for DS	$k_{DS} = 45 \cdot (1 - 0.0014 \cdot (DS - 45))$	(30)	1
pH correction	$k_{pH} = \left(1 + 0.3 \cdot \left(\frac{pH_{in} - pH_{out}}{2} - 7.5\right)\right)$	(31)	1
Flowrate F	$F = F_0 \cdot \exp(-k_d \cdot t)$	(32)	1
Activity, Act	$Act = 0.926 \cdot \frac{F\rho}{w} \frac{DP}{100} \cdot X_{eq} \cdot k_{DS} \cdot k_{pH} \cdot \ln\left[\frac{X_{eq}}{X_{eq}}\right.$	(33)	1
Productivity, P	$P = \frac{\int F[S]_0 \, dt}{w}$	(34)	1
Total Number of Eq.			**32**

*The Flowrate is the variable which is varied during the operation in order to keep the substrate conversion (X_s) constant and is calculated using Eq. (32). In that case it can be seen that all the variables in the Eq. (28) are constant except the flowrate and the activity, so in order to keep the conversion constant the flowrate needs to decay at the same rate as the activity decays. The enzyme activity decay is given in dimensionless form in the Eq. (3).

For the model analysis the systematic procedure proposed by Gani et al. [214] has been used. The total number of equations (balance equations and constitutive equations) are listed in Table 5.51. The model consists of 21 ODEs, 32 (explicit) AEs, the total number of variables is 82 and the number of the variables to be specified is 29. Table 5.51 gives the degree of freedom analysis.

Table 5.51 Degree of Freedom analysis of the GI reactor model.

Type of equation	Number of equations
ODEs	21
Algebraic	32
Total number of variables	82
Degree of Freedom	29

Table 5.52 lists all variables of the GI reactor model, the variables to be specified have been classified as system variables, system parameters and as known variables. The variables to be calculated have been classified as algebraic variables, which are the variables, needed for the calculation of the right-hand side of the differential equations in order to calculate the dependent variables.

Table 5.52 Variables classification of the glucose isomerization reactor model.

	Variables Types	Symbol	Number of Variables	Total Number
To be specified	System Variables	w, θ, $[S]_0$, d_p, F_0, ε, ρ, μ, d_b, H, D_m, ρ_{cat}, DS, pH_{in}, pH_{out}, DP, R_p, $X_{i,}$	18	
	System Parameters	A_{kmf}, A_{kmr}, A_{vmf}, A_{vmr}, A_d, E_{kmf}, E_{kmr}, E_{vmf}, $E_{vmr,}$ E_d,	10	
	Known Variables	R	1	29
To be calculated	Algebraic (explicit)	T, v_{mf}, v_{mr}, k_{mf}, $k_{mr,}$ $k_{d,}$ K_{eq}, X_{eq}, V_m, K_m, A, U_0, Re_p, Sc, D_L, R_s, Pe, Q_4, Q_1, D_s, Q_2, Q_3, φ, k_L, α, X, Act, y_{eq}, P, F, k_{DS}, k_{pH}	32	
	Dependent Variables	$\underline{y_S}$, $\underline{y_s^*}$, y_E	21	53

Typical values of the variables listed in Table 5.52 are given in Table 7.33 in Appendix D.

5.4.3.3 Phase III. Model Identification/Discrimination

The values of the system parameters for the reactor model, have been obtained from the literature. The kinetic parameters (A_{kmf}, A_{kmr}, A_{vmf}, A_{vmr}, E_{kmf}, E_{kmr}, E_{vmf}, E_{vm}, A_d, E_d) have been taken from [205] and they are listed in TABLE the Appendix D. The parameters for the enzyme decay (A_d, E_d) found in published papers are given in Table 5.53, which are to be evaluated through experimental data provided by Novozymes A/S.

Table 5.53. Different parameter sets found in the published literature for the enzyme inactivation kinetics.

	[202]	[215]	[216]	[206]
Enzyme	**Sweetase**	**Sweetase**	**Sweetzyme T**	**Sweetzyme T**
Parameter	**Set A**	**Set B**	**Set C**	**Set D**
A_d (d^{-1})	1.82×10^{25}	1.51×10^{25}	3.26×10^{25}	1.09×10^{26}
E_d($J\ mol^{-1}$)	170969.10	170867.75	174710.40	176464.65

The experimental data is provided from Novozymes A/S, and shows the enzyme activity with respect to time for the different temperatures (55°C-90°C). However, because the data is not reliable for temperatures above 70°C, the model is to be evaluated considering the experimental data at temperature range 55-70°C. The process operation conditions are given in Table 7.34 in Appendix D and the experimental data is presented in Figure 5.28.

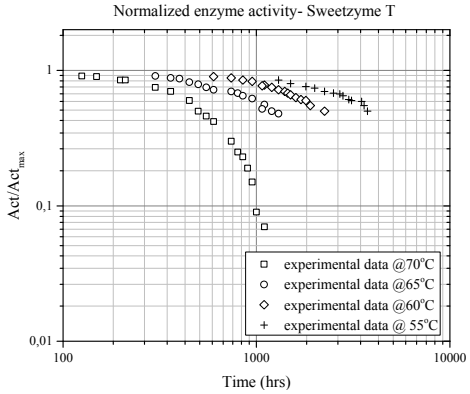


Figure 5.30 Enzyme activity with respect to time for temperature range 55-70°C. Enzyme: Sweetzyme T. Experimental data is provided by Novozymes A/S.

In Figure 5.29-Figure 5.32, the experimental data together with the model prediction for different parameter sets (listed in Table 5.53) for different temperatures are presented. In the beginning, the experimental data at 55°C is compared with the model prediction. The results are presented in Figure 5.29, and it can be seen that the model prediction using the parameter set A and B is in good agreement with the experimental data while the model calculation using the parameter set C and D are not in good agreement with the experimental data.

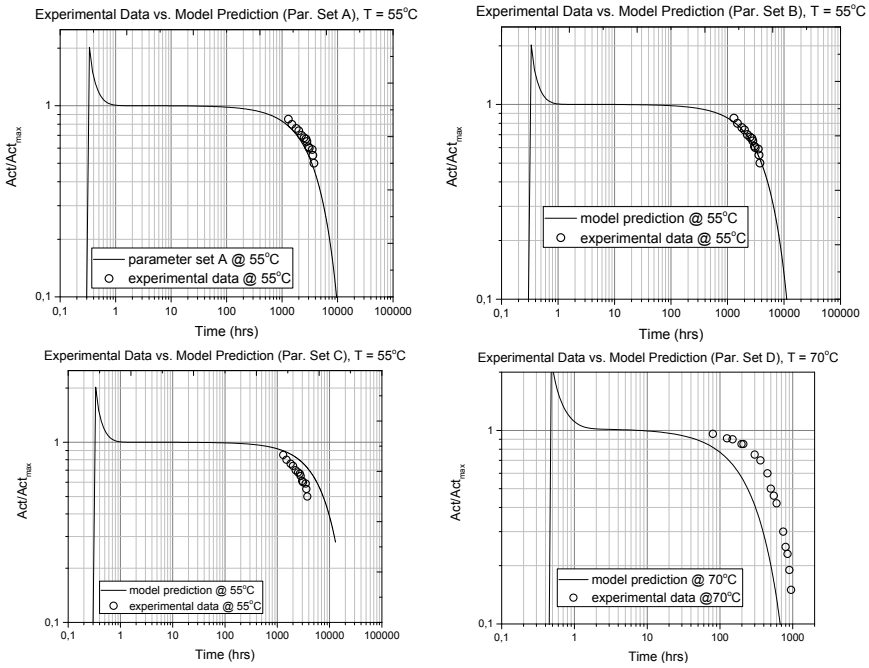


Figure 5.31 Model prediction vs. experimental data at 55°C for parameters set A-Dgiven in Table 5.53.

The experimental data at 60°C is then compared with the model calculation for the different parameter sets. The results are presented in Figure 5.30, and it can be seen that the model calculation using the parameter set C is in good agreement with the experimental data while model calculation using the parameter set A, B and D are not in good agreement with the experimental data.

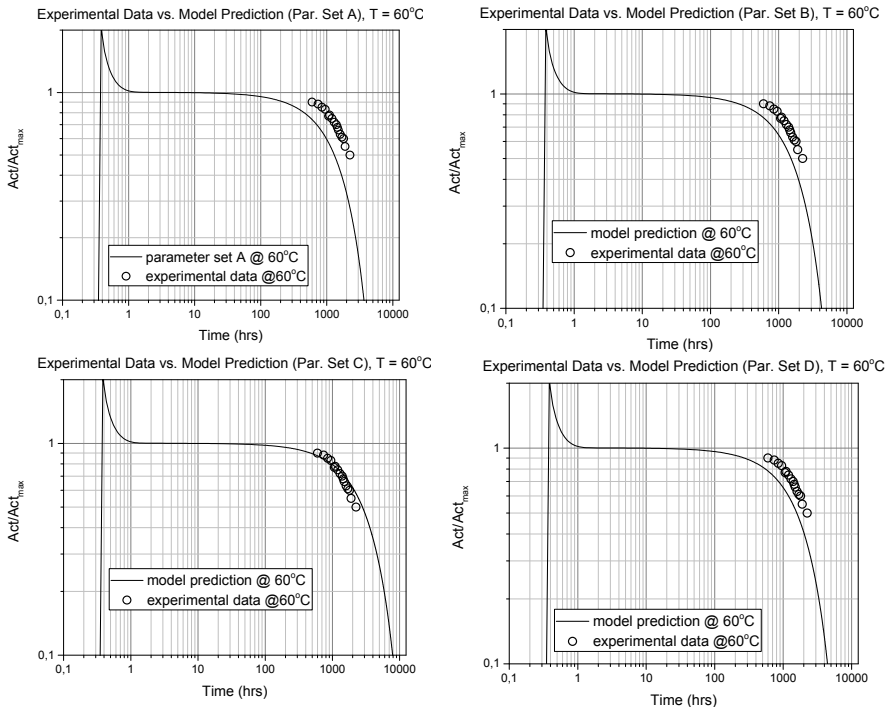


Figure 5.32 Model prediction vs. experimental data at 60°C for parameters set A-D given in Table 5.53.

The experimental data at 65°C is compared with the model prediction for the different parameter sets. The results are illustrated in Figure 5.31, and it can be seen that the model prediction using the parameter set C is in good agreement with the experimental data while model prediction using the parameter set A, B and D are not in good agreement.

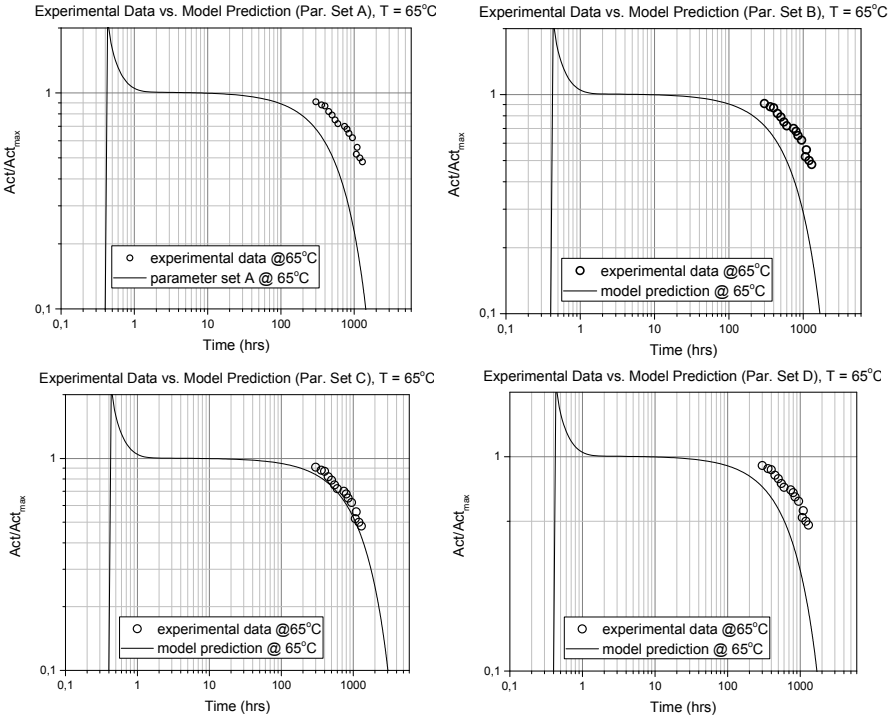
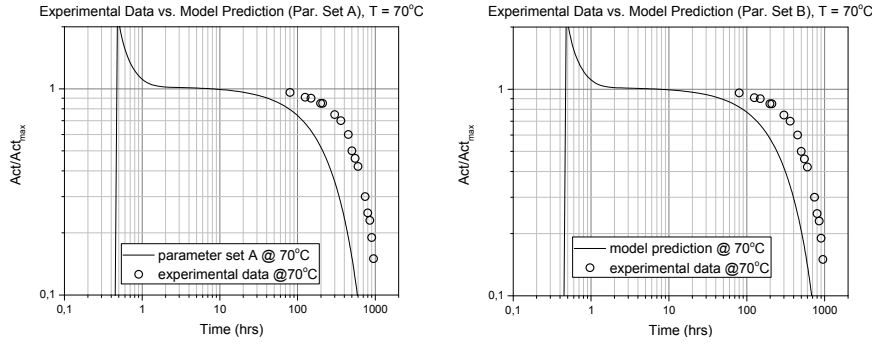


Figure 5.33 Model prediction vs. experimental data at 65°C for parameters set A-D given in Table 5.53.

The experimental data at 70°C is compared with the model prediction for the different parameter sets. The results are illustrated Figure 6, and it can be seen that the model prediction using the parameter set C is in good agreement with the experimental data while model prediction using the parameter set A, B and D are not in good agreement.



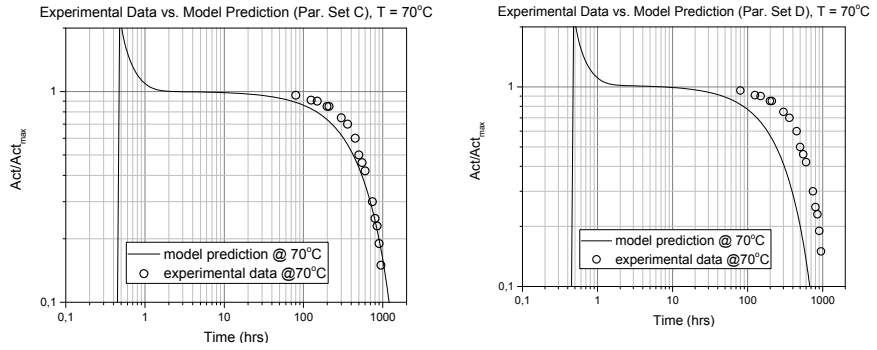


Figure 5.34 Model prediction vs. experimental data at 70°C for parameters set A-D given in Table 5.53

5.4.3.3.1 Fine tuning the parameters A_d and E_d.

Figure 5.29-Figure 5.32 compare the model prediction to the experimental data for a temperature range 55°C-70 °C for different inactivation parameter sets (given in Table 5.53). From the analysis, it can be noticed that the different parameter set can provide better or worse matching with the experimental data, therefore it is essential to fine-tune the parameters A_d and E_d in order to have a set of parameters that provides acceptable model prediction for the certain temperature range (55-70°C). For the fine tuning six experimental data points (given in Table 5.54), the initial enzyme activity and the half time activity for operating temperature 55°C, 60°C and 70°C, are going to be used. The experimental set for 65°C is going to be used as validation for the fine-tuned parameters.

Table 5.54 Experimental data used in fine-tuning the inactivation parameters A_d and E_d.

Operation Temperature	Time	Amax (IGU/gr enzyme)	t½ (hrs)	A (IGU/gr enzyme)
T = 55 °C	0	195	3750	97.5
T = 60 °C	0	262	2200	131
T = 70 °C	0	503	500	251.5

Based on the data from Table 5.54 , the parameters have been fine-tuned their values are given inTable 5.55.

Table 5.55 Enzyme deactivation parameters Ad and Ed found in literature and the fine-tuned parameters.

	[202]	[215]	[216]	[206]	**This project**
Enzyme	**Sweetase**	**Sweetase**	**Sweetzyme T**	**Sweetzyme T**	**Sweetzyme T**
Parameter	**Set A**	**Set B**	**Set C**	**Set D**	**Fine-tuned**
A_d (d^{-1})	1.82×10^{25}	1.51×10^{25}	3.26×10^{25}	1.09×10^{26}	3.08×10^{16}
E_d(J mol^{-1})	170969.10	170867.75	174710.40	176464.65	118491

The fined-tuned parameters are evaluated against the experimental data and the results of the fine-tuning are presented in Figure 5.33.

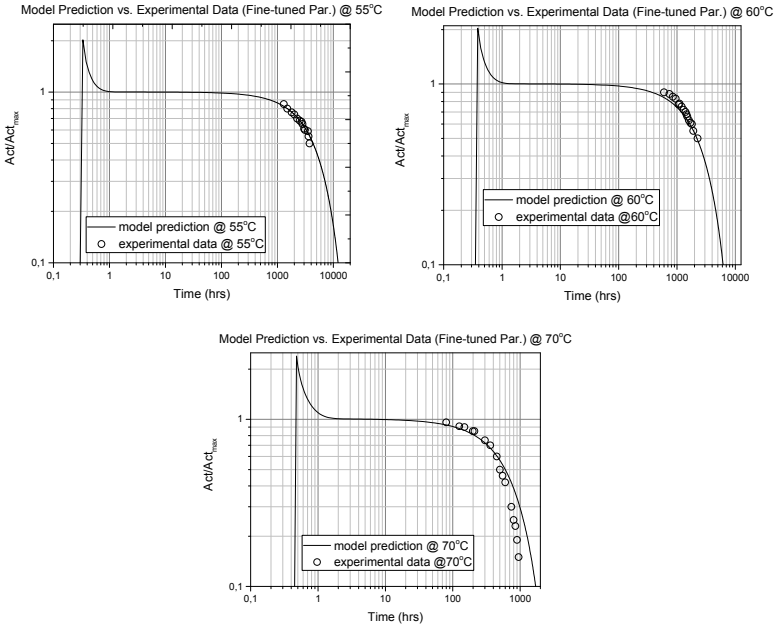


Figure 5.35 Model prediction vs. experimental data at temperatures 55, 60 and70°C using the fine-tuned parameters.

As it is illustrated in Figure 5.33, the model prediction fits very well the experimental data. The next step now is the model validation

5.4.3.4 Model Evaluation/Validation

The remaining set of experimental points (at operating temperature 65°C) is used now for the validation of the model using the fined-tuned parameters. Figure 5.34 illustrates the model prediction and the experimental data at 65°C and it can be seen that the model can sufficiently describe the experimental measurements. The model is now validated and it can be used for simulations in the operating temperature range 55-70°C.

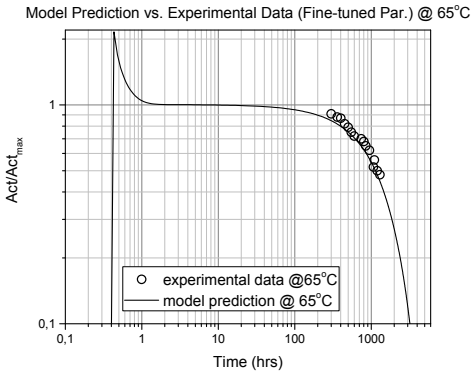


Figure 5.36. Model prediction versus the experimental data at 65°C using the fine-tuned parameters.

5.4.4 Section C: Separation synthesis

The separation of fructose from the reaction mixture is fixed in this process. Therefore, Section C is not investigated.

5.4.5 Section D: Process Simulation, Evaluation and Operation

Step D.1. Process simulation and evaluation

Simulation I. Reactor Performance vs. Temperature. The objective of this simulation-based study is to determine the range of the operation temperature of the reactor. The process operation conditions used in this simulation are given in Table 7.35 (in Appendix D). The simulation is performed for different operation temperatures while the substrate concentration is kept constant for all the simulations. The reactor is operated at constant substrate conversion of 42% for 1.5 yr. without temperature increase during the operation.

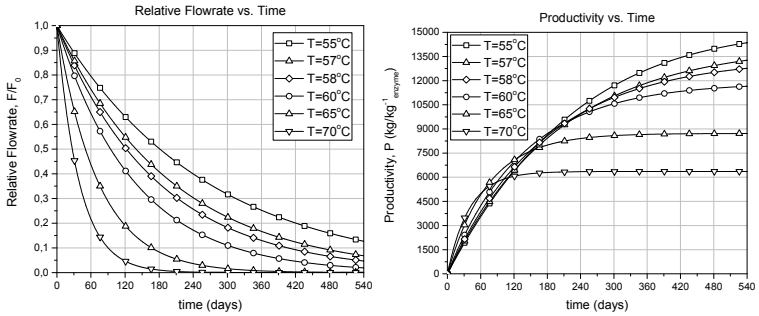


Figure 5.37 Relative flowrate and productivity of the GI reactor for different operating temperatures. Constant substrate conversion 42%. The process conditions are given in Table 7.34 (in Appendix D).

The reactor model provides qualitatively correct and consistent results for different operating temperatures as highlighted in Figure 5.35. It can be noted that the production rate is higher when the temperature increases but also the enzyme activity (it can be seen from the relative inlet flowrate plot) decreases rapidly at high temperatures resulting in much lower productivity.

Table 5.56 Model prediction for the maximum enzyme activity, enzyme half-life, 10% 15% and the productivity for different operating temperatures.

Operation	A_{max} (IGU/gr enzyme)	$t_{½}$ (days)	$t_{10\%}$ (days)	$t_{15\%}$ (days)	P (kg/kg enzyme)
T = 55°C	195	180	505	433	14356
T = 57°C	215	137	385	329	13267
T = 58°C	232	119.5	335	288	12766
T = 60°C	261	91.5	256	220	11652

Step D.2 Process Optimization/control/monitoring and validation

During the operation, the initial operating temperature is kept constant until the time that the measured remaining activity is at 10-15% of the initial enzyme activity, then in order to burn-out the remaining enzyme the temperature increases. In this step, the temperature change during the operation is done by considering a step change in the temperature profile. As it had been shown in Simulation I, the system is very sensitive to the operating temperature as it can affect the enzyme activity, the question now is whether the process performance can be improved when the temperature is increased by (1-2°C) during the operation?

Simulation II. Temperature profile during the operation

To investigate the effect of the temperature profile during the operation, four operational scenarios have been defined and the results are compared with the base case scenario. The scenarios are given in Table 5.57.

Table 5.57 Operational scenarios to test the effect of temperature during the reaction.

	Initial temperature	Temperature profile
Base Case	55°C	Constant, when remaining activity is at 15% temperature increases to 65°C
Scenario 1	55°C	1°C every 100 days, when remaining activity is at 15% temperature increases to 65°C
Scenario 2	55°C	2°C every 200 days, when remaining activity is at 15% temperature increases to 65°C
Scenario 3	55°C	Operation at 55°C for 200 days, temperature increase by 2°C every 100 days after 200 days, when remaining activity is at 15% temperature increases to 65°C
Scenario 4	55°C	temperature increase by 1°C every 100 days for the first 300 days, then temperature increase 2°C every 100 days, when remaining activity is at 15% temperature increases to 65°C

Considering the operation scenario defined in Table 5.57, the simulations were performed considering one reactor and the process conditions are given in Table 7.34 (in Appendix D). The simulation results are highlighted in Figure 5.36-Figure 5.37, where the enzyme activity and the corresponding temperature change are presented. Looking at the enzyme activity plots in Figure 5.36-Figure 5.37, the enzyme decay during the operation can be observed. In all the scenarios the picks in the enzyme activity profiles can be noticed, these picks are because when the temperature increases at a specific operating time, it causes the increase in the enzyme

activity but also the enzyme decay is accelerated. The corresponding step-changes in operating temperature for each scenario are illustrated below each of the enzyme activity plots in Figure 5.36-Figure 5.37.

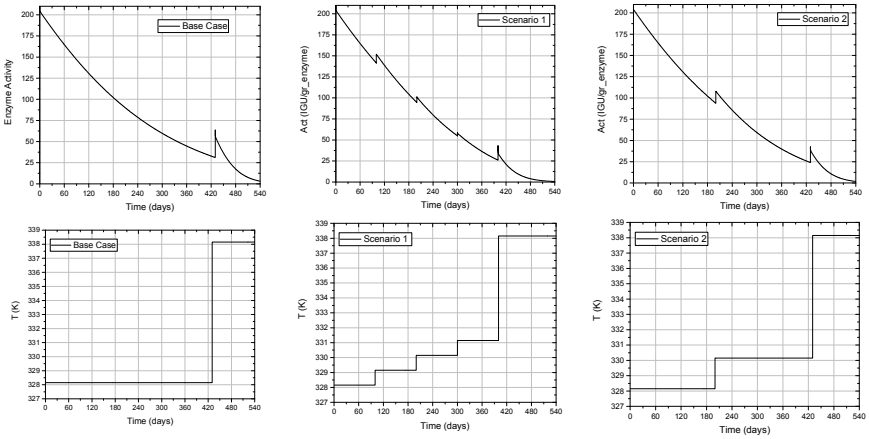


Figure 5.38 Enzyme activity as the function of time and the corresponding temperature change (Base case, scenario 1, scenario 2).

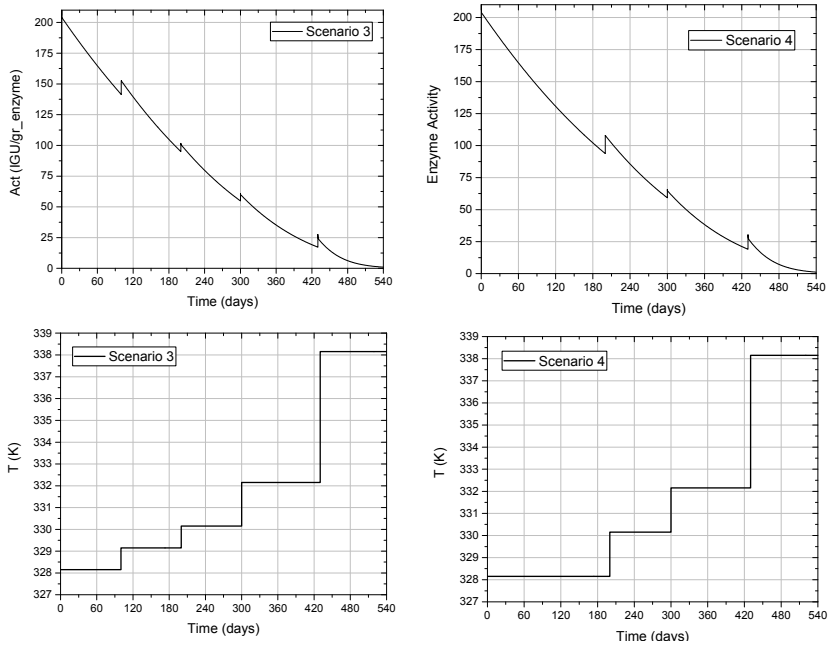


Figure 5.39 Enzyme activity as the function of time and the corresponding temperature change (scenario 3 and scenario 4).

The productivity for the operational scenarios of Table 5.57 is shown in Figure 5.38 where it can be seen that the base case scenario is performing better than the rest and that scenario 2 is performing well but not better than the base case. It can also be noticed in Figure 5.38 that the productivity for all the scenarios is higher than the productivity in the base case at operating time between 130-400 days, this is because when the temperature increases, the activity increases and the productivity rate also increases. However, at the end of the operation, the productivity is higher in the base case scenario because the overall enzyme inactivation in the base case was slower compared to the enzyme inactivation in the rest of the scenarios.

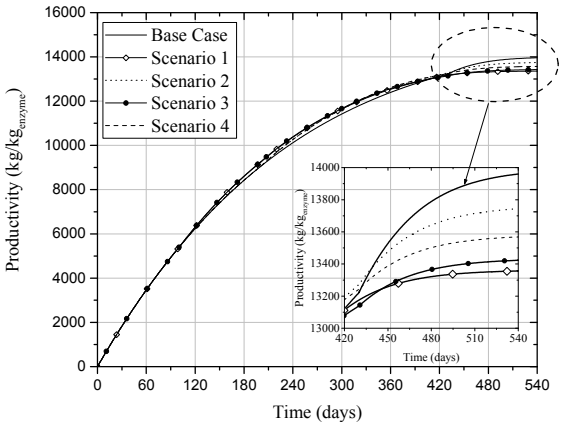


Figure 5.40 The productivity for the operational scenarios given in Table 5.57.

Step D.3 Process Operation

The validated reactor model is now used to simulate a typical GI reactor plant, which consist of 20 parallel fixed bed reactors. Due to the enzyme inactivation, the reactor productivity rate is allowed to gradually decrease until the complete depletion of the enzyme activity. In order to maintain a steady state operation, the reactors are started at different time; this time difference is called "age distribution". Therefore, the first reactor starts at time 0, then the second reactor starts after time t (age distribution) and so on.

Simulation III. Reactor Plant (20 reactors).

The simulation considers 20 reactors where the age distribution between each reactor is 27 days, each reactor operates for 1.5 year (540 days) from the starting point of each reactor, after the 540 days of operation the reactor stops and it is assumed that the reactor is restarted 2 days after its shutdown, finally, the total simulated operation of the plant is assumed for 4 years (1440 days). The reaction temperature is fixed at 55^{o}C and as it has been explained before, when the remaining activity is 15% of the initial the temperature increases by a step change in the model to 65^{o}C for the complete burn-out of the enzyme. The process conditions are given in Table 7.35 (in Appendix D)**.** The results are highlighted in Figure 5.39, where the productivity per reactor and the total productivity of the reactor plant are presented. In Figure 5.39 (plot on the left) the productivity of each reactor is shown, it can be seen the different starting point of each reactor, the increase in productivity rate when the temperature increases

and finally the reactor shut-down and its restart. On the plot on the right hand side, the total productivity of the reactor plant, which is the summation of the productivity of each reactor with respect to time, is shown.

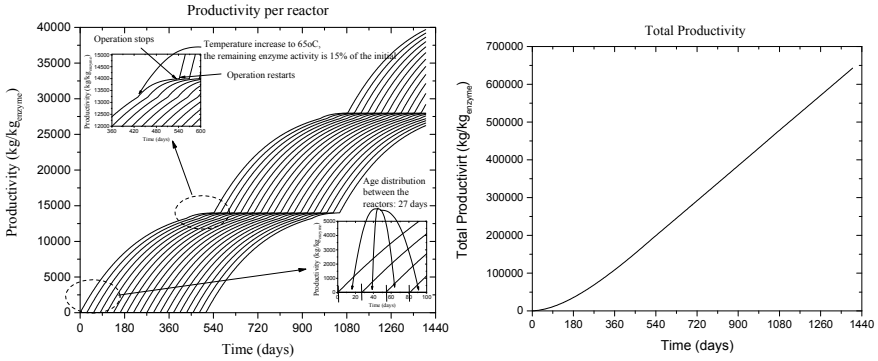


Figure 5.41 Productivity per reactor as a function of the time, the age distribution, the temperature increase and the reactor are presented (figure on the left). Total productivity of the reactor plant (figure on the right).

Figure 5.40 illustrates the average daily productivity of the plant that is the difference of the productivity between two days (plot on the left-hand side), it can be seen that the system reaches the steady state when all the reactors are in operation. During the operation, the average daily productivity increases when a reactor starts and decreases because of the enzyme inactivation. Figure 5.40 also illustrates the average daily reactor productivity where it can also be seen that after 1.5 year of operation, the productivity of the plant has reached the steady state. The deviation in the average daily productivity when the reactor plant has reached the steady state is 11%.

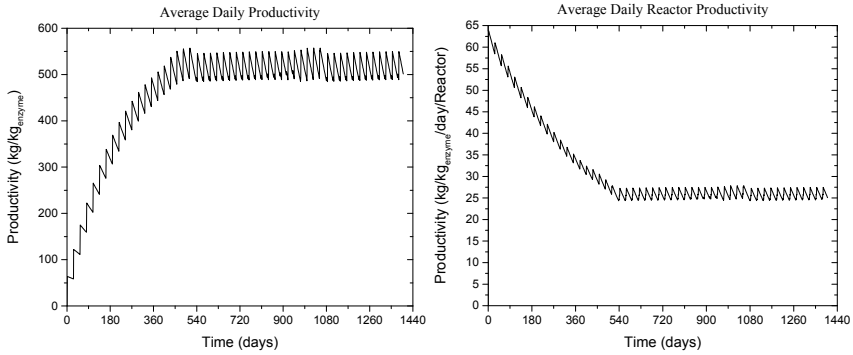


Figure 5.42 The average plant productivity (figure on the left) with maximum deviation of 11% and the average daily reactor productivity (figure on the right).

5.4.6 Conclusions

A multi-scale reactor model to describe the glucose isomerization process has been developed within a framework for systematic mathematical model development. In one scale the model takes into account the enzyme decay, the reaction kinetics and the substrate diffusion in the

enzymatic pellet as a function of the temperature and is connected with the other scale that is the flow in the fixed-bed reactor. To validate the model experimental data provided by Novozymes A/S for the enzyme activity of the Sweetzyme T A/S was used. Model-based analysis performed to determine the operating temperature and the temperature profile during the glucose isomerization operation. Finally, the reactor model was used to simulate a typical GI reactor plant where 20 reactors are operated in parallel.

6 CONCLUSIONS AND FUTURE PERSPECTIVES

6.1 Conclusions

In this project, an integrated framework consisted of systematic model-based methods for pharmaceutical process development during their early stage development focusing on the production of small molecule pharmaceutical active ingredients has been developed. The objective has been to generate the required process knowledge to enhance the process understanding, to assist with process improvements at the early process development stages and to investigate opportunities for continuous manufacturing. Process system engineering (PSE) methods and tools, which have been successfully applied to other industries, such as the chemical and the petrochemical industry, have been integrated in the framework and extended when necessary to include process concerns related to the pharmaceutical processes.

6.2 Main contributions

The main contributions of this project are discussed.

6.2.1 Integrated Framework

The framework is able to deal with the development of processes to produce small molecule APIs for completely new batch or continuous processes, and to retrofit already existing processes, with known or unknown state-task network or flowsheet. The framework is integrated with systematic model-based methods and tools such as databases, modelling libraries, process synthesis methods, solvent selection/design/analysis tool, mathematical modelling tools and process evaluation tools, which are used to generate data to assist the decision making process and evaluate different process alternatives. The framework has been divided into four main sections related to process development of pharmaceutical active ingredients starting with the reaction pathway identification, the reaction analysis, the separation synthesis and finally, process evaluation and optimization.

6.2.2 Reaction pathway identification

A database based on organic reactions and biochemical reactions, which provides a data-rich environment, has been developed for reaction pathway identification, where knowledge can be collected, stored, and retrieved. The focus of this database is in pharmaceutical processes and multiphase reactions taking place within the pharmaceutical industry, which are associated with processing information. The reactions in this database have been categorized in terms of the reaction type, target product to be produced (when single-step or multistep reactions are considered), reaction product, and effect of the solvent use in the reacting system. Information that are contained in the database is reaction conditions (temperature, pressure etc.), reaction compound (reagents, catalysts etc.), reaction data (conversion, selectivity, dynamic data set, and kinetic models), scaling information and finally batch or continuous processing. For each reaction entry, a description of the process exists and the references are provided.

6.2.3 Solvent Selection

6.2.3.1 Solvent Swap methodology

A systematic methodology for solvent swap problems in pharmaceutical processes has been developed and has been integrated with overall developed framework. Using this methodology a list of feasible solvent candidates suitable for the swap task is generated based on criteria for good solvent swap and phase equilibrium analysis. The generated solvents for the swap task are further analysed taking into account the desired solvent properties for the next processing task. Thus, the list of the feasible solvent candidates is reduced and consists of solvents that are suitable for the swap and the subsequent operational task. The selected solvents are validated for the swap task through rigorous dynamic simulation of batch distillation operations that perform the swap task. The final selection of the swap solvent is made by analysis of the simulation results that also help to establish operational criteria and to compare the performance of different candidates as the swap solvent.

6.2.3.2 Solvent Swap database and computer-aided tool

A solvent swap database consisting of 21 solvents that are commonly used in pharmaceutical processes has been created. The database provides the necessary property values, calculated apriori for us in the second step of the methodology. The database can also be used as a quick and reliable guide for fast solvent selection for the swap process. In addition, the solvent swap method and associated tools have been integrated in a computer-aided tool integrated with ICAS-SolventPro.

6.2.4 Batch to continuous

Opportunities of converting batch to continuous have been investigated in this project through the analysis of unit operations operated in batch mode. Crystallization and reaction are the unit operations that are commonly used in batch mode while the rest of unit operations such as distillation and liquid-liquid extraction are compatible in both continuous and batch mode. Through process analysis, the process limitations have been identified and designs, which can be used to overcome these limitations, have been proposed through an information-based system. In this project, a database with data on continuous and batch unit operations that are commonly used in pharmaceutical process has been developed. The database contains information such as the processing part, operation mode, types of unit operation, primary and secondary properties and finally operation and design properties. For a given set of processing

concerns, the database can be used to propose whether or not an operation can be performed in a continuous or batch operation.

In this project, investigation of batch to continuous operation was performed for the production of ibuprofen (case study 1) and for the production of L-2-aminobutyric acid (case study 3). In the first case study, the continuous operation of the first reaction step was identified using the unit operation database. For the second and third reactive steps, the benefits of continuous reaction were identified and designs were proposed. In the third case study, a continuous multiphase enzymatic membrane reactor (EMR) identified to replace the batch operation. A mathematical model, based on reaction kinetics was developed to evaluate the EMR design compared to batch one. For the final verification of the suggested designs, model-based methods and/or experimental validation are required.

6.2.5 Reaction analysis and process synthesis

In this project, great emphasis was given on the reaction analysis and the process synthesis. Performing the reaction analysis, limitations related to the performance of the reaction can be identified and solutions to overcome these limitations are suggested, for example, implementation of different reactor technologies, solvent selection and/or reaction conditions optimization. The results of reaction analysis are used to make important decisions for the reactor design, for recycle streams, possibilities of reaction telescoping, possibilities of intensified reaction-separation, to identify needs for solvent swap and defining the separation needs when a separation is needed.

Process synthesis methods and tools have used in this project to identify the type of unit operation and to generate process alternatives that satisfy the separation objectives. In the separation analysis, the efficiency of unit operation is determined by detailed equilibrium analysis or information from literature (for example membranes), solvent selection is also performed when is required and the need for solvent swap is identified.

6.2.6 Model-based analysis, design and operational improvements

In this project, systematic modelling approaches based on first principles were developed and applied in the case studies. Model-based methods were used in the ibuprofen case study to evaluate the reaction kinetics in terms of reaction performance in different reaction conditions. Model-based methods were also applied to evaluate feasibility of continuous the enzyme multiphase membrane reactor that applied for the reaction-separation system presented in the case study 3. Finally, model-based analysis through simulations was performed for the industrial case of glucose isomerization where the enzyme performance and operation planning were evaluated for different operational scenarios without the need of performing new experiments, which in this case is very time consuming. Therefore, model-based methods can be used to perform analysis and evaluation of the system of interest, to perform optimization studies to improve the process performance, to evaluate different design and to assist and improve the operation planning.

6.2.7 Process evaluation

Process evaluation to be used as a measure for the selection of different processing alternatives, process designs, and reaction pathways has been integrated in the overall framework.

Possibilities for improvements have been identified by the process evaluation analysis and can be translated to optimization targets.

6.3 Future perspectives

The efforts to improve the pharmaceutical processes have dramatically increased over the years. In this project, some key research areas related to pharmaceutical process development have been investigated. However, there are many research fields, which require further investigation and development. In this section some of the research areas where application and development of process systems engineering methods and tools are needed, are discussed.

Framework limitations and challenges. The implementation of the framework requires the use of model-based methods and tools to generate data. During the application of the framework several limitations and challenges might be faced related to available data, data generation and the use of model-based tools. A first limitation appears during the application of the reaction analysis section (section B of the framework) where a kinetic model is important to evaluate the effect of different process variables on the reaction performance and perform reaction optimization. However, the reaction models need first to be developed and then validated using experimental dynamic reaction data, that might be time consuming or difficult to generate. Moreover, kinetic models are required as the basis of reactor models to be rapidly used to evaluate different scenarios of the reactive system such as different reactor configurations or reactor types. Other limitations are related on using model-based methods to predict the phase behaviour (VLE, LLE and SLE) of multicomponent mixtures containing molecules with complex functional groups such as to predict the solubility of API in different solvent mixtures. In addition, process evaluation in terms of sustainability and economics might be difficult to be implemented because the lack of sustainability data for pharmaceutical compounds and the lack of data to develop reliable cost models for the newly developed technologies. To conclude, the framework needs to adopt additional predictive model-based tools or to expand the already developed ones in order to reduce the time required to perform additional experiments and consequently the time required to implement the framework. In this section, different areas within the framework where data gaps do exist and the adoption of tools is required is discussed in detail.

Reaction improvement and analysis. Advances in reaction synthesis can lead in significant advances in pharmaceutical processes, as the reactions are the core of these processes. Extension of the developed database, with many more reactions and processing information is required to create an even richer data environment at the early stage process development. This process knowledge can be used as an input to computer-aided tools that can perform the retrosynthesis, to investigate and evaluate different processing alternatives. Another aspect of the reaction synthesis is the selection of the substrates suitable for specific reaction types. The selection of the optimum substrate might lead in acceleration of pharmaceutical reactions to enable continuous synthesis, reduction of solvent required, increased process safety and improvement in separation process by reducing the number of steps resulting in greener, safer and high product quality processes.

Mathematical models, which are predictive in nature and can be used to evaluate pharmaceutical processes during the development phases are required. Dynamic models to describe most of the unit operations already exist and they are coupled with predictive thermodynamic models. However, new models for newly developed technologies such as

microreactor technology might need to be developed, and stored in the framework for their easy retrieval and reuse. These dynamic models can be used to improve the process understanding of the processes and be applied for process optimization, for evaluation of different operational scenarios (e.g. start-ups and shutdowns) and finally for evaluation and implementation of different control strategies. A limitation here might be in the currently available thermodynamic models that might not able to describe the functional groups of some of the molecules. In this case, experimental data and parameter regression would be needed.

Process analytical technology (PAT) is widely used to supplement process knowledge by collecting data in-line to enhance the process understanding in order to improve pharmaceutical processes development and minimize risks. The selection of the proper process analytical technology has been studied by Singh et al. [177] based on a knowledge-based system which has to be extended to include more pharmaceutical processes such as reaction (using different technologies) and continuous crystallizion.

Process intensification in pharmaceutical processes can have a high impact on the process development as production volume, environmental impact, production cost and energy requirements might be decreased. However, the advantages of process intensification must be shown in many cases, as the introduction of complicated equipment, especially, in a production line, might be problematic due to high investments risks that are associated with the implementation of process intensification equipment. Other concerns are related to the short product life and the simplicity of the multipurpose pharmaceutical batch processing.

LCA analysis. Emphasis should be given in the evaluation of the life cycle assessment (LCA), which can be used to evaluate the environmental impact from the extraction of the raw material to the final disposal of drug and to identify possibilities for process improvements. A major limitation here, is that the life cycle inventory (LCI) databases should be updated with data for pharmaceutical compounds.

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NOMENCLATURE

Symbols	*Description*	*Units*
c_i or[i]	Concentration of compound i	kmol/m^3
t	time	time units
V_{ij}	Stroichiometric coeffienet of the compound i in j reaction	
K	Equilibrium constant	
kj	Kinetic parameter of reaction j	Depending on the reaction order
P	Pressure	atm
P_i	Partial pressure of i	atm
H_e	Henry constant	kmol/m^3/MPa
A_j	Preexponentation factor of the reaction j	Depending on the reaction order
Ea	Activation energy	J/mol
R	Universal gas constant	8.314 J/mol/K
T	Temperature	K
$\alpha_{i/j}$	Relative volatility	-
α_{aver}	Average relative volatility	-
P	Pressure	atm
ΔH^{fus}	Enthalpy of fusion	kJ/mol
γ	Activity coefficient	-
ξ	Separation factor	-
ee%	Enantiomeric selectivity	
C	conversion	
S	selectivity	
V	Volume	
F	Flowrate	Amount (moles. Vol., mass) /time
J	flux	
k	Mass transfer coefficient	
π	pi number	8.314
Pi	Partition coefficient	
MW	Molecular weight	gr/mol
SolPar	Solubility parameter	$MPa^{1/2}$
y_i	Dimensionless concentration for enzyme and substrate	-
y_s*	Dimensionless concentration for the substrate in the pellet	-
t	Time	min
r_j	Reaction rates	mol m^{-3} min^{-1}
S	Substrate, glucose	-
E	Enzyme	-
SE	Complex which is formed between the enzyme and the substrate	-

P	Product, fructose	-
w	Catalyst load	$gr_{cat}\ m^{-3}$
V_m	Maximum apparent reaction rate	$mol\ gr_{cat}^{-1}\ min^{-1}$
K_m	Apparent Michaelis-Menten constant	$mol\ m^{-3}$
k_{mf}	Michaelis Constant for the forward reaction (glucose to fructose)	$mol\ m^{-3}$
k_{mr}	Michaelis Constant for the reserve reaction (fructose to glucose)	$mol\ m^{-3}$
v_{mf}	maximum reaction rates for the forward reaction (glucose to fructose)	$mol\ gr_{cat}^{-1}\ min^{-1}$
v_{mr}	maximum reaction rates for the reserve reaction (fructose to glucose	$mol\ gr_{cat}^{-1}\ min^{-1}$
k_d	Deactivation constant	min^{-1}
θ	Temperature	^oC
k_{eq}	Equilibrium constant	-
X	Conversion of the substrate	-
X_{eq}	Equilibrium conversion	-
d_b	Bed Diameter	m
U_0	Superficial velocity	$m\ min^{-1}$
A	Reactor Cross section area	m^2
F_k	Inlet flowrate for the reactor k (= 1, 2, …NR)	$m^3\ hr^{-1}$
Re_p	Particle Reynolds number	-
Sc	Schmidt number	-
D_m	Molecular Diffusivity	$m^2\ min^{-1}$
D_L	Dispersion Coefficient	$m^2\ min^{-1}$
Pe	Peclet Number	-
r	Pellet radius $0<r<R_p$	m
τ	Dimensionless time	-
D_s	Molecular diffusivity	$m^2\ min^{-1}$
R_p	Particle radius	m
k_1	Dimensionless variable	-
Q_i	Dimensionless variables (i=1, 2, 3, 4)	-
Greek Letters		
μ	viscosity	$kg\ m\ min^{-1}$
ε	Bed porosity	-
ρ	Density	$kg\ m^{-3}$
λ	Dimensionless pellet radius	-
ξ	Dimensionless reactor length	
Φ	Thiele modulus	-
α	Dimensionless mass transfer	-
Vol.%	Volumetric composition	%
Subscripts		
m	Melting point	
i	Compound i	

OS	Original solvent
SwapS	Swap solvent
S	Solute
tot	Total
t=0	Initial time
eq	At Equilibrium
NR	Total Number of Reactions
p	particle
b	Fixed bed
S	substrate
cat	Catalyst
aq	Aqueous
Org	Organic
Abbreviations	
VLE	Vapour-Liquid Equilibria
PSE	Process systems engineering
PAT	Process analytical technology
QbD	Quality by design
NCE	New chemical entities
CSD	Crystal size distribution
MSMPR	Mixed suspension mixed product removal
PBE	Population balance equations
DEM	Discrete element method
PBM	Population balance model
LCA	Life cycle assessment
VOC	Volatile organic compounds
NR	Number of reactions
SFILES	Simplified Flowsheet Input Line Entry System
CSTR	Continuous stirred tank reactor
PFR	Plug flow reactor
ICAS	Integrated computer aided system
NSAID	Nonsteroidal anti-inflammatory drugs
IBB	Isobutylbenzene
4-IBAP	4-isobutyl acetophenone
API	Active pharmaceutical ingredient
CAMD	Computer-aided modelcular design
ω-TA	ω-transaminase
ODE	Ordinary differential equation
AE	Algebraic equation
PDE	Partial differential equation
SLE	Solid-Liquid Equilibria
LLE	Liquid-Liquid Equilibria
DCM	Dichloromethane
MTBE	Methyl tert-butyl ether

ACTN	Acetone
ANSL	Anisole
MeOH	Methanol
THF	Tetrahydrofuran
EtAC	Ethyl acetate
MeTHF	Methyltetrahydrofuran
MEK	Methyl ethyl ketone
MeCN	Acetonitrile
IPA	2-propanol
IPAc	Isopropylacetate
MIBK	Methyl-isobutyl-ketone
DMF	N,N-Dimethylformamide
NMP	N-Methyl pyrrolidone
EtOH	Ethanol
n-BuOH	1-butanol
i-BuOH	2-methyl-1-propanol (iso butanol)
CXX	Conditional swap number XX
VE (or I)	Very easy swap
EA (or II)	Easy swap
DF (or III)	Difficult swap
VD (or IV)	Very difficult swap
IP (or V)	Impossible swap
AP	Aprotic polar
HBD	Hydrogen bond donor
AALP	Aromatic apolar or highly polar
EPD	Electorn pair donor
AAA	Aliphatic aprotic apolar

7 APPENDIX

A. Calculation related to Case study 1

A-I Section A: Reaction pathway

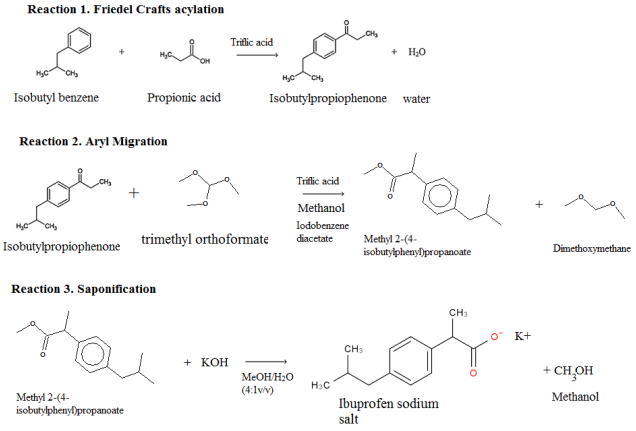
	N	Reaction Type	Reactant 1	Reactant 2	Reactant 3	Reactant 4	Product 1	Product 2	Product 3	Product 4	Phases Involved	How phases are created?	Solvent Classification
1	9	Carbonylation	C12H18O (1-(4-isobutylphenyl) ethanol)	CO	-	-	C13H18O2 (Ibuprofen)	-	-	-	L (org) - L (aq) - G	water	water
2	10	Carbonylation	C12H18O (1-(4-isobutylphenyl) ethanol)	CO	-	-	C13H18O2 (Ibuprofen)	-	-	-	L (org) - G	Organic Solvent	Ketone
3	13	Carbonylation	C12H18O (1-(4-isobutylphenyl) ethanol)	CO	-	-	C13H18O2 (Ibuprofen)	-	-	-	L-L	water	water
4	44	Saponification	C14H20O2 (Methyl 2 - (4 - isobutylphenyl)pro...	KOH (Kallium hydroxide)	-	-	ibuprofen (C13H18O2)	CH3KO (pottasium methoxide)	-	-	Liquid	Organic Solvent	Alchohol
5	45	Friedel Crafts acylation	Isobutylbenzene (C10H14)	propionyl chloride (C3H5ClO)	AlCl3	-	4-isobutylpropiophenone (C13H18O)	HCl	AlCl3	-	L(org)-L(aq)	water	water
6	46	1,2-aryl migration	C13H18O (4-isobutylpropiophenone)	C4H10O3 (trimethyl orthoformate)	-	-	C14H18O2 (Methyl 2 - (4 - isobutylphenyl)pro...	C3H8O2 (Dimethoxymethane)	-	-	Liquid	Organic Solvent	Formide/alcohol
7	47	Saponification	C14H21O2 (Methyl 2 - (4 - isobutylphenyl)pro...	C2H6OS (2-mercaptoethanol)	NaOH	-	C13H18O2 Na (Ibuprofen sodium salt)	CH3OH (MeOH)	-	-	Liquid	Solvent Mixture	Achohol/water
8	67	Friedel Crafts acylation	(C10H14) isobutylbenzene	C4H6O3 (acetyl anhydride)	-	-	C12H16O (4-isobutyl acetophenone)	C2H4O2 (acetic acid)	-	-	L(org)-L(aq)	HF	HF
9	68	Hydrogenation	C12H16O (4-isobutyl acetophenone)	H2 (Hydrogen)	-	-	C12H18O (isobutyl phenyl ethanol)	-	-	-	L(org)-G	Solvent+H2	Alcohol
10	69	Hydrogenation	C12H16O (4-isobutyl acetophenone)	H2 (Hydrogen)	-	-	C12H18O (isobutyl phenyl ethanol)	-	-	-	L(org)-Gas	H2	-
11	70	Hydrogenation	C12H16O (4-isobutyl acetophenone)	H2 (Hydrogen)	-	-	C12H18O (isobutyl phenyl ethanol)	-	-	-	L(org)-Gas	Solvent+H2	Alcohol
12	71	Hydrogenation	C12H16O (4-isobutyl acetophenone)	H2 (Hydrogen)	-	-	C12H18O (isobutyl phenyl ethanol)	-	-	-	L(org)-G	Solvent+H2	Alcohol
13	72	1,2-aryl migration	C13H18O (4'-Isobutylpropiophenone)	C4H10O3 (trimethyl orthoformate)	-	-	C14H20O2 (Methyl 2 - (4 - isobutylphenyl)pro...	C3H8O2 (Dimethoxymethane)	-	-	L(org)	solvent	Alcohol
14	73	Fridel Crafts acylation	(C10H14) isobutylbenzene	Propionic acid (C3H6O2)	-	-	C13H18O (4'-Isobutylpropiophenone)	H2O	-	-	L (org)	-	-
15	74	Fridel Crafts acylation	(C10H14) isobutylbenzene	mixture of acetylating agents: C2H4O2 (acetic ac...	C2H3FO (acetyl fluoride)	-	C12H16O (4-isobutyl acetophenone)	H2O	HF	-	L(org)-L(aq)	HF	HF
16	75	Hydrogenation	C12H16O (4-isobutyl acetophenone)	H2 (Hydrogen)	-	-	C12H18O (isobutyl phenyl ethanol)	-	-	-	L(org)-G	solvent	alchohol

	MainProduct	Reaction info	Solvent Function	Solvent	Temperature	Pressure	Stoichiometry	Base	Acid	pH	Catalyst	Residence time	Conversion (%)	Selectivity	Yield	Process Yield
1	Ibuprofen	Ibuprofen Synthesis (Step 3)	Creates second phase, catalyst soluble in water ...	water	388K	54 bar	NULL	CHECK	CHECK	CHECK	Pd catalyst	check	20%	98%	19%	n.i.
2	Ibuprofen	Ibuprofen Synthesis (Step 3)	Dissolve Reactants/Catalyst	MEK	140oC	2000psig	-		-	-	0.08 mol% Pd catalyst	2hr	99%	95.5%	94.1%	n.i.
3	Ibuprofen	Ibuprofen Synthesis (Step 3)	Creates second phase, catalyst soluble in water ...	water	130oC	2400 psig	-	-	75 mol% HCl	-	0.007 mol% PdCl2, ligand: 0.08 mol% PPh3	155min	99%	96.6%	95.6%	-
4	Ibuprofen	Synthesis of Ibuprofen (Step 3)	Dissolves reactants	MeOH/H2O (4:1 v/v)	65oC	-	1:20	-	-	-	-	3min	-	-	70%	51%
5	Ibuprofen	Synthesis of Ibuprofen (Step 1)	Dissolves reactants	water	70oC	250psi	1:1.17:1.11	-	1 M HCl	4.5	-	1.25 min	99%	100	99%	>90%
6	Ibuprofen	Synthesis of Ibuprofen (Step 2)	Dissolves reactants, promoter	DMF/n-propanol	70oC	250psi	1:8	-	-	-	3 ICl (iodine monochloride)	2.5 min	-	-	90%	-
7	Ibuprofen	Synthesis of Ibuprofen (Step 3)	Dissolves reactants	MeOH/Water (1:3 v/v)	90oC	250psi	-	-	-	-	-	3min	-	-	92%	-
8	Ibuprofen	Synthesis of Ibuprofen (Step 1)	creates second phase, extract the product	HF	80oC	Pressure to prevent HF to volatilize	1:2	-	50 eq. HF	acidic	HF	3 hr	85%	81%	-	-
9	Ibuprofen	Synthesis of Ibuprofen (Step 2)	Dissolves reactants	Methanol	30oC	6.8 atm	1	-	-	-	5 wt% palladium/carbon cata lyst	1 hr	99.5%	96.6%	-	-
10	Ibuprofen	Synthesis of Ibuprofen (Step 2)	-	-	60oC	17 atm	1	-	-	-	Activated Ni sponge	1.5 hr	99.8%	-	-	-
11	Ibuprofen	Synthesis of Ibuprofen (Step 2)	Dissolves reactants	Methanol	60oC	8.16 atm	1	-	-	-	Pd/CaCO3	18 hr	85%	100%	-	-
12	Ibuprofen	Synthesis of Ibuprofen (Step 2)	Dissolves reactants	Methanol	60oC	8.16 atm	1	-	-	-	Pd/C with triethyl amine	1hr	97%	100%	-	-
13	Ibuprofen	Synthesis of Ibuprofen (Step 2)	Dissolves reactants	Methanol	50oC	-	1:4	-	5 eq.TrOH (triflic acid)	-	1 eq. iodobenzene diacetate	2 min	98%	-	96%	-
14	Ibuprofen	Synthesis of Ibuprofen (Step 1)	-	-	150oC	1 atm	1:1	NULL	5 eq. TrOH	-	TrOH	10 min	92%	-	74%	-
15	Ibuprofen	Synthesis of Ibuprofen (Step 1)	creates second phase, extract the product	HF	60-70oC	40-60 psig (prevent solvents to boil)	1:2 (v/v)	-	-	-	HF	3hr	25.6%	100%	25.6%	-
16	Ibuprofen	Synthesis of Ibuprofen (Step 2)	dissolves reactants	Ethanol	70oC	20bar	1	-	-	-	0.5-3.0 wt% Na- 3wt% (of substrate) Pd/C	2-9hr	>90%	96.4%	96.9%	-

Experimental data	Kinetic model	Mode	Comments	References	Application
c vs. time	kinetic model available	Batch	-	Chaudhari et al. 2004	Pharma
Initial and end points	no	Batch	-	Elango et al. 1987	Pharma
Initial and end points	no	Batch	-	Elango et al. 1987	Pharma
Steady state data for different conditions	-	Flow	-	Bogdan et al.2009	Pharma
Steady state data for different conditions	-	Flow	by products are removed in the aqueous phase whi...	Sneal et al. 2015	Pharma
-	-	Flow	acetone was added in - line to quench residual di...	Sneal et al. 2015	Pharma
Steady state data for different conditions	-	Flow	-	Sneal et al. 2015	Pharma
Initial and end points	no	batch	-	Elango et al. 1991	Pharma
Initial and end points	no	batch	-	Elango et al. 1991	Pharma
Initial and end points	no	batch	-	Ryan et al. 1990	Pharma
-	-	batch	-	Seaki et al. 1990	Pharma
-	-	batch	-	Seaki et al. 1990	Pharma
Steady state data for different conditions	-	flow	-	Bogdan et al. 2009	Pharma
Steady state data for different conditions	-	flow	-	Bogdan et al. 2009	Pharma
steady state data	no	continous	-	Lindley et al. 1991	Pharma
c vs. time	Already developed model is used	batch	-	Cho et al. 2013	Pharma

Figure 7.1 Reaction type database results when it is search for "Main Product = Ibuprofen"

Bogdan et al. Reaction pathway for ibuprofen synthesis



Sneal et al. Reaction pathway for ibuprofen synthesis

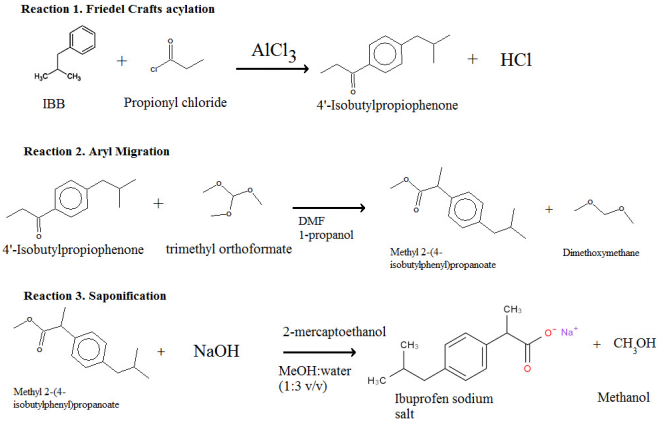


Figure 7.2. Recently published reaction pathway for ibuprofen synthesis as they have been retrieved using the reaction type database.

A-II Section B. Reaction analysis

Model for the carbonylation reaction

Phase II: Model construction

Table 7.1 Reaction mechanism considered for the development of the carbonylation model

No of Reaction	Reaction	Comments
1.	$IPBE + H^+ \xrightarrow{k_1} IBS + H_3O^+$	Production of the intermediate IBS (D) from the substrate IPBE(B)
2.	$IBS + H^+ + Cl^- \underset{k_3}{\overset{k_2}{\rightleftarrows}} IBPCl$	Production of the active intermediate IBPCl (E) from B
3.	$IBPCl + CO + H_2O \xrightarrow[k_4]{PdCl_2(PPh_3)_2(C_1)} [IBN + 3IPPA] + H^+ + Cl^-$	Production of Ibuprofen (IBN) and the main impurity 3-IPPA (P1+P2=P) from E

Table 7.2 Mass balance equations for the carbonylation step

Compound	Mass balance	
IBPE (B)	$\frac{dc_B}{dt} = -r_1$	(35)
IBS (D)	$\frac{dc_D}{dt} = r_1 - r_2 + r_3$	(36)
IBPCl (E)	$\frac{dc_E}{dt} = r_2 - r_3 - r_4$	(37)
IBN+3-IPPA(P)	$\frac{dc_P}{dt} = r_4$	(38)

Table 7.3 Constitutive equations for the carbonylation step

No of Reaction	Reaction Rate	
1	$r_1 = k_1 c_B c_{H^+}$	(39)
2	$r_2 = k_2 c_D c_{H^+} c_{Cl^-}$	(40)
3	$r_3 = k_3 c_E$	(41)
4	$r_4 = \frac{k_4 c_E c_{H_2O} A^* c_1^m}{1 + K c_E}$	(42)
5	$k_i = A_i^{ref} \exp\left[-\frac{E_{a,i}}{RT_K}\right]$	(43)

Table 7.4 Model anaylsis for the kinetic model of the carbonylation step

Type of equation	Number of equations	Equation number

ODE equations	4	(35)-(38)
Algebraic	9	(39)-(42)and 4x(43)
Total number of variables	38	
Degree of Freedom	25	

Table 7.5 Variables values for the kinetic model of the carbonylation step

Depedent variable	***Initial Value***	***Source***	***Comments***
c_B	0.562-2.248kmol m^{-3}	[37]	
c_D	0	[37]	
c_E	0	[37]	
c_P	0	[37]	
System Parameters	***Value***	***Source***	***Comments***
k_1	Table 7.7	[37]	The kinetic parameters regressed for different temperatures and the pre exponential factor and activation energy will be calculated
k_2	Table 7.7	[37]	
k_3	Table 7.7	[37]	
k_4	Table 7.7	[37]	
System Variables	***Value***	***Source***	***Comments***
c_{cat}	1.121x10^{-3}-4.482x10^{-3} kmol m^{-3}	[37]	-
c_{H+}	0.224-0.896 kmol m^{-3}	[37]	-
c_{H2O}		[37]	-
c_{CL-}	0.224-0.896 kmol m^{-3}	[37]	-
t	60 min	[37]	-
P_{CO}	3.4-7.48 MPa	[37]	-
H_e	Table 7.6**Error! Reference source not found.**	[37]	-
R	8.314	[37]	-
T_K	378K-398K	[37]	-
m	0.43	[37]	-
K	0.51	[37]	-

Table 7.6 The Henry coefficient values of CO in a mixture of IBPE/MEK [37].

Mixture of IBPE and MEK (w/w %)	**H_ex10^3 (kmol/m^3/MPa)**		
	378K	*388K*	*398K*
11% of IBPE	6.131	6.444	6.735
22% of IBPE	5.579	5.798	6.311
33% of IBPE	5.051	5.479	5.906

Table 7.7 Regressed parameters using ICAS-MoT, carbonylation step.

Kinetic parameter	**378K**	**388K**	**398K**
k_1 x 10^2 [m^3 $kmol^{-1}$ sec^{-1}]	1.30 ± 9.04 x 10^{-2}	1.62 ± 1.60 x 10^{-1}	1.80 ± 1.88 x 10^{-1}
k_2 x 10^2 [(m^3 $kmol^{-1}$)^2 sec^{-1}]	7.64 ± 5.29 x 10^{-1}	12.70 ± 1.25	10.40 ± 1.08
K_3 x 10^2 [m^3 $kmol^{-1}$ sec^{-1}]	0.43 ± 2.98 x 10^{-2}	0.89 ± 8.74 x 10^{-2}	0.28 ± 2.90 x 10^{-2}
k_4 [(m^3 $kmol^{-1}$)$^{2.43}$$sec^{-1}$]	1.03 ± 7.17 x 10^{-2}	1.05 ± 0.104	1.82 ± 0.19

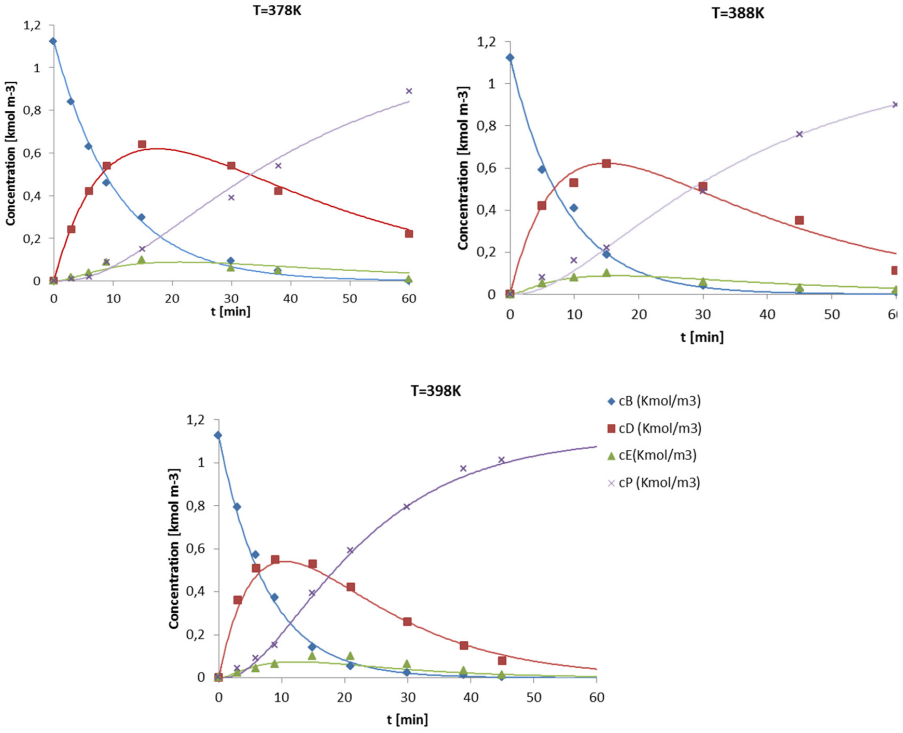


Figure 7.3 Model prediction against experimental data for different temperatures IBPE 1.123kmol m^{-3}, TsOH/LiCl (1:1) 0.121 kmol m^{-3}, PCO 5.4MPa, $PdCl_2(PPh_3)_2$ 1.121 x 10^{-3} kmol m^{-3}, PPh_3 2.242 x 10^{-3} kmol m^{-3}, water 2.67 kmol m^{-3}, MEK 1.95 x 10^{-5} m^3.

A-III Section C. Separation process synthesis

For the Friedel-Crafts acylation step, the compounds involved in reaction together with some of their pure compound properties are listed in Table 5.10.

Table 7.8. Pure compound properties for the compound involved in reaction step 1 (Friedel crafts acylation).

Compound	Role	Formula	MW (gr mol^{-1})	Sol.Par. [298K]	Tb (K)	Tm (K)	Ref
Isobutylbenzene (B)	Reactant	$C_{10}H_{14}$	134.22	17.27	445.94	221.70	CAPEC database
Acetic anhydride (F)	Reactant	$C_4H_6O_3$	102.09	22.01	412.70	200.15	CAPEC database
Hydrofluoric acid (A)	Cat/solvent	HF	20.01	15.59	292.67	189.79	CAPEC database
Acetic acid (D)	By-product	$C_2H_4O_2$	60.05	19.01	391.05	289.81	CAPEC database

Acetyl fluoride (E)	By-product	C_2H_3FO	62.04	19.55	295.64	201.76	ProPred
4-isobutyl acetophenone (C)	Prod/react	$C_{13}H_{18}O$	190.28	17.98	550.73	285.62	ProPred

Azeotropic information are listed in Table 5.11, three azeotropes have been identified.

Table 7.9 Binary azeotropes obtained from CAPEC database

Binary Azeotropes	**Tb [K]**	**P[atm]**	**X_1**	**X_2**	**Method**
Acetic acid/isobutyl benzene	434.71	3.3	0.97	0.03	Predicted using UNIFAC

Based on the pure compound properties the binary ratio matrix has been constructed (see Table 5.12)

Table 7.10 Binary ratio matrix (Friedel crafts acylation)

Binary pair	**Mw**	**T_b**	**T_m**	**SolPar**	**H^{Fus}**	**P^{vap}**	**H^{vap}**	**VdV**	**DP**	**RG**	**Mv**
HF/IBB	6.71	1.52	1.17	1.11	2.73	461.74	6.44	9.92	5.84	22.66	7.55
HF/4-IBAP	9.51	1.88	1.50	1.15	2.78	44944.25	8.17	20.66	1.18	∞	8.97
HF/HoAc	3.00	1.34	1.53	1.22	2.56	58.76	3.03	3.66	1.05	12.99	2.75
HF/AcF	3.10	1.01	1.06	1.25	-0.09	1.11	3.25	∞	∞	∞	3.07
HF/Ac_2O	5.10	1.41	1.05	1.41	2.29	185.45	6.30	5.98	1.53	17.81	4.53
IBB/4-IBAP	1.42	1.23	1.29	1.04	1.02	97.34	1.27	2.08	4.94	∞	1.19
IBB/HoAc	2.24	1.14	1.31	1.10	1.07	7.86	2.13	2.71	5.58	1.75	2.74
IBB/AcF	2.16	1.51	1.10	1.13	-0.03	415.53	1.98	∞	∞	∞	2.46
IBB/ Ac_2O	1.31	1.08	1.11	1.27	1.19	2.49	1.02	1.66	8.94	1.27	1.66
4-IBAP /HoAc	3.17	1.41	1.01	1.06	1.08	764.84	2.70	5.64	1.13	∞	3.26
4-IBAP /AcF	2.16	1.51	1.10	1.13	-0.03	415.53	1.98	∞	∞	∞	2.46
4-IBAP /Ac_2O	1.86	1.33	1.43	1.22	1.21	242.35	1.30	3.45	1.81	∞	1.98
HoAc /AcF	1.03	1.32	1.44	1.03	-0.04	52.88	1.07	∞	∞	∞	1.11
HoAc / Ac_2O	1.70	1.06	1.45	1.16	1.12	3.16	2.08	1.63	1.60	1.37	1.65
AcF / Ac_2O	1.65	1.40	1.01	1.13	-24.26	166.89	1.94	∞	∞	∞	1.48

Based on the listed possible separation task (see Table 7.4 identified using Table 7.3), the objectives of the separation and process conversations. For the reaction step 1, the first separation after the reaction, there are two phases, the IBB rich phase and the HF rich phase, which contains the product. In this way, the IBB rich phase can be recycled back in the reactor and azeotropic separations are avoided.

Table 7.11 Feasible separation tasks for Friedel crafts acylation

Task	**Separation Technique**

HF/IBB	Flash, Distillation, Prevaporation, Liquid membranes, Ultrafiltration
HF/4-IBAP	Flash, Distillation, Crystallization, Ultrafiltration
HF/HoAc	Flash/Striping, Distillation, Crystallization, Liquid membranes, Ultrafiltration
HF/AcF	Distillation, Ultrafiltration
IBB/4-IBAP	Distillation, Flash, Crystallization
IBB/HoAc	Distillation, Crystallization, Liquid membranes, Ultrafiltration
IBB/AcF	Distillation, Flash operation, Ultrafiltration
4-IBAP /HoAc	Distillation, Flash operation, Ultrafiltration,
4-IBAP /AcF	Distillation, Flash operation, Ultrafiltration,
HoAc /AcF	Distillation, Flash operation, crystallization

By combining the separation tasks, the list of separation process alternatives is generated and listed in Table 5.13.

Table 7.12 Generated process flowsheets (Firedel-Crafts reaction) where A: HF, B: IBB, C: IBAP, D: AcOH, E: AcF, F: Ac_2O

	Generated SFILES
1	(iB)(iAC)(rABC/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(dsAE/FBC)2[oFDBC](dsFDB/C) [oFDB][oC]
2	(iB)(iAC)(rABC/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(dsAEFD/BC)2[oBC](dsB/C)[oB][oC]
3	(iB)(iAC)(rABC/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(dsA/BCDEF)2(dsEFD/BC)[oEFD] [oBC](dsB/C)[oB][oC]
4	(iB)(iAC)(rABC/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(dsAEFD/BC)2[oBC](crB/C) [oB][oC]
5	(iB)(iAC)(rABC/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(dsAEFD/BC)2[oBC](fB/C) [oB][oC]
6	(iB)(iAC)(rABC/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(prevA/BCDEF)2[oBCDEF](dsEFDB/C) [oEFDB][oC]
7	(iB)(iAF)(rBFDE/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(prevA/BCDEFF)2[oBCDEF] (prevBCDEF/F)[oBCDEF](fE/DFBC)[oE][oFBC](D/FBC5[oFBC](FB/C)[oC](crysB/C)[oC][oB]
8	(iB)(iAF)(rBFDE/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(prevA/BCDEFF)2[oBCDEFF] (prevBCDEF/F)[oBCDEF](fE/DFBC)4(D/FBC)5[oFBC](fFB/C)6[oC](fB/C)7[oC]
9	(iB)(iAF)(rBFDE/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(prevA/BCDEFF)2[oBCDEFF] (prevBCDEF/F)[oBCDEF](fE/DFBC)4(DF/BC)5[oBC](B/C)6[oC]
10	(iB)(iAF)(rBFDE/pABCDEF)<1<2(llspB/ABCDEF)1(oABCDEF)(prevA/BCDEFF)2[oBCDEFF] (prevBCDEF/F)[oBCDEF](fE/DFBC)4(DF/BC)5[oBC](crysB/C)6[oC]
11	(iB)(iAF)(rBFDE/pABCDEF)<1<2 (llspB/ABCDEF)1(oABCDEF)(prevA/BCDEFF)2[oBCDEFF] (prevBCDEF/F)[oBCDEF](fE/DFBC)4(DF/BC)5[oBC](fB/C)6[oC]
12	(iB)(iAF)(rBFDE/pABCDEF)<1<2 (llspB/ABCDEF)1(oABCDEF)(prevA/BCDEFF)2[oBCDEFF] (prevBCDEF/F)[oBCDEF](fE/DFBC)4(DFB/C)5[oC]
13	(iB)(iAF)(rBFDE/pABCDEF)<1<2 (llspB/ABCDEF)1(oABCDEF)(prevA/BCDEFF)2[oBCDEFF] (prevBCDEF/F)[oBCDEF](fE/DFBC)4(fDFB/C)5[oC]
13	(iB)(iAF)(rBFDE/pABCDEF)<1<2 (llspB/ABCDEF)1(oABCDEF)(prevABCDEF/F)[oABCDEF] (prevA/BCDEF)3[oBCDEF](fE/DFBC)4(D/FBC)5[oFBC](F/BC)6[oBC](B/C)7[oC]

Table 7.13 Generated SFILES for the sectond reactive step (Hydrogenation Step, solvent-free reaction)

	Generated SFILES
1	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(E/CB) [oCB](C/B)[oC]
2	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(E/CB)[oFCB](C/B)[oB][oC]
3	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(E/CB)[oFCB](C/B)[oB][oC]
4	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(E/CB)[oE][oCB](C/B)[oC][oB]
5	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(EC/B)[oEC](E/C)[oE][oC]
6	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(EC/B)[oEC](E/C)[oE][oC]
7	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(EC/B)[oEC](E/C)[oE][oC]
8	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(EC/B)[oEC]crys(E/C)[oE][oC]
9	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(EC/B)[oEC](prevE/C)[oE][oC]
10	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(EC/B)[oEC](prevE/C)[oE][oC]
11	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(EC/B)[oEC](prevE/C)[oE][oC]
12	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(EC/B)[oEC](prevE/C)[oE][oC]
13	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)(EC/B)[oEC](lmemE/C)[oE][oC]
14	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)prevE/CB[oE][oCB](C/B)[oB][oC]
15	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)prevE/CB[oE][oCB](C/B)[oB][oC]
16	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)prevE/CB[oE][oCB](C/B)[oB][oC]
17	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)lmemE/CB[oE] [oCB](C/B)[oB][oC]
18	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)lmemE/CB[oE][oCB](C/B)[oB][oC]
19	(iA)(iB)(rAB/pABCE)(fA/ECB)(oECB)lmemE/CB[oE][oCB](C/B)[oB][oC]

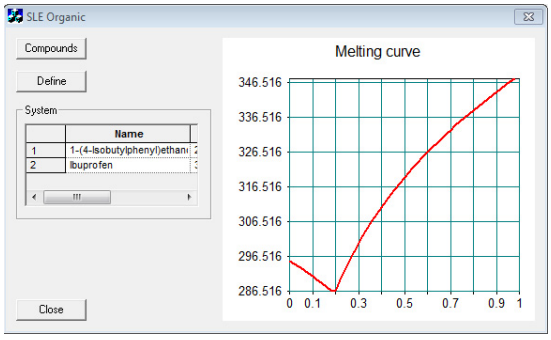


Figure 7.4 Solid-liquid equilibrium of Ibuprofen and IPBE

Solvent evaluation for different crystallization solvent for ibuprofen crystallization is illustrated in Figure 7.5

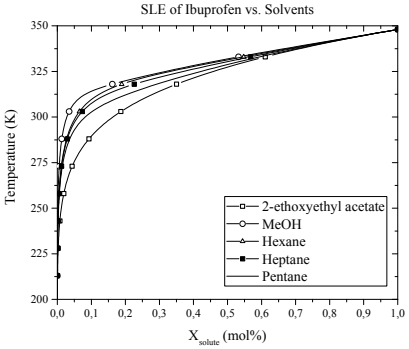


Figure 7.5 Solid-liquid equilibrium for Ibuprofen in different solvents. Calculated using ICAS-SolventPro

A-IV Section D. Process evaluation/optimization

The mass and energy balances for the carbonylation step, are given in Table 7.8-Table 7.10.

Table 7.14 Mass and Energy balances for crabonylation step (Part A)

			Reactor 3		CO removal				Liquid liquid extraction			
		Units	**inlet**	**outlet**	**inlet**	**separation factor**	**top**	**bottom**	**inlet**	**separation factor**	**top**	**bottom**
	Phase	-	G-L-L	G-L-L	G-L-L	-	G	L-L	L-L		L(org)	L(aq)
	Temperature	K	393	393	393	-	393	393	350		350	350
	Pressure	bar	54	54	1	-	1	1	1	-	1	1
	Enthalpy	kJ/kmol	2048.330	-8567.820	-8555.250	-	111.010	-8584.670	8655.290		-10287.683	-5009.676
	Required energy	MJ		8.614		-		0.000				0.019
	Compounds											
1	isobutylbenzene	kg/hr	0.0036	0.0036	0.0036	0.000	0.0000	0.0036	0.0036	0.000	0.0000	0.0036
2	Acetic anhydride	kg/hr	0.0000	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
3	Hydrofluoric acid	kg/hr	0.0000	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
4	Acetic acid	kg/hr	0.0000	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
5	Acetyl fluoride	kg/hr	0.0000	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
6	4-isobutyl acetophenone	kg/hr	0.0000	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
7	Hydrogen	kg/batch	0.0000	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
8	iso-butyl phenyl ethanol	kg/batch	86.8877	0.4344	0.4344	0.000	0.0000	0.4344	0.4344	0.000	0.0000	0.4344
9	4-isobutylethylbenzene	kg/batch	0.0122	0.0122	0.0122	0.000	0.0000	0.0122	0.0122	0.000	0.0000	0.0122
10	water	kg/batch	4.2840	4.2840	4.2840	0.000	0.0000	4.2840	4.2840	0.920	3.9413	0.3427
11	CO	kg/batch	13.6463	0.0682	0.0682	1.000	0.0682	0.0000	0.0000	0.000	0.0000	0.0000
12	2-ethoxyethylacetate	kg/batch	0.0000	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
13	Ibuprofen	kg/batch	0.0000	96.6302	96.6302	0.000	0.0000	96.6302	96.6302	0.000	0.0000	96.6302
14	3-(4-isobutylphenyl)propanoic acid	kg/batch	0.0000	0.6002	0.6002	0.000	0.0000	0.6002	0.6002	0.000	0.0000	0.6002
15	1-(4-isobutylphenyl)ethyl chloride	kg/batch	0.0000	1.9079	1.9079	0.000	0.0000	1.9079	1.9079	0.000	0.0000	1.9079
16	HCL	kg/batch	0.0284	0.3820	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
17	4-isobutylstyrene	kg/batch	0.0000	0.6217	0.6217	0.000	0.0000	0.6217	0.6217	0.000	0.0000	0.6217
	Mass	kg	104.862	104.944	104.562		0.068	104.494	104.494	0.920	3.941	100.553
	Total mass	kg					104.562				104.494	

Table 7.15 Mass and Energy balances for crabonylation step (Part B)

			Crstallization solvent addition	Crystallization				Drying			
		Units	**addition**	**inlet**	**separation factor**	**top**	**bottom**	**inlet**	**separatio**	**top**	**bottom**
	Phase	-	L (org)	L (org)		S-L	L	S-L		G	S
	Temperature	K	350	350		298	298	298		430	430
	Pressure	bar	1	1		1	1	1		1	1
	Enthalpy	kJ/kmol	-3548.131	-7237.000		-12178.012	-5227.852	-12178.012		1612.942	-8053.735
	Required energy	MJ	1.405				1.180				-1.800
	Compounds										
1	isobutylbenzene	kg/hr	0.0000	0.0036	0.000	0.0000	0.0036	0.0000	0.000	0.0000	0.0000
2	Acetic anhydride	kg/hr	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
3	Hydrofluoric acid	kg/hr	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
4	Acetic acid	kg/hr	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
5	Acetyl fluoride	kg/hr	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
6	4-isobutyl acetophenone	kg/hr	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
7	Hydrogen	kg/batch	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
8	iso-butyl phenyl ethanol	kg/batch	0.0000	0.4344	0.000	0.0000	0.4344	0.0000	0.000	0.0000	0.0000
9	4-isobutylethylbenzene	kg/batch	0.0000	0.0122	0.000	0.0000	0.0122	0.0000	0.000	0.0000	0.0000
10	water	kg/batch	0.0000	0.3427	0.000	0.0000	0.3427	0.0000	0.000	0.0000	0.0000
11	CO	kg/batch	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
12	2-ethoxyethylacetate	kg/batch	39.6792	39.6792	0.010	0.3968	39.2824	0.3968	1.000	0.3968	0.0000
13	Ibuprofen	kg/batch	0.0000	96.6302	0.792	76.5408	20.0894	76.5408	0.000	0.0000	76.5408
14	3-(4-isobutylphenyl)propanoic acid	kg/batch	0.0000	0.6002	0.144	0.0867	0.5135	0.0867	0.000	0.0000	0.0867
15	1-(4-isobutylphenyl)ethyl chloride	kg/batch	0.0000	1.9079	0.000	0.0000	1.9079	0.0000	0.000	0.0000	0.0000
16	HCL	kg/batch	0.0000	0.0000	0.000	0.0000	0.0000	0.0000	0.000	0.0000	0.0000
17	4-isobutylstyrene	kg/batch	0.0000	0.6217	0.000	0.0000	0.6217	0.0000	0.000	0.0000	0.0000
	Mass	kg	39.679	140.232	0.947	77.024	63.208	77.024	1.000	0.397	76.627
	Total mass	kg				140.232				77.024	

Table 7.16 Mass and Energy balances for crabonylation step (Part C)

			Solvent recovery -water removal				Solvent recovery -solvent removal			
		Units	inlet	separatio	top	bottom	inlet	separation	top	bottom
	Phase	-	L		L	L	L		L	L
	Temperature	K	298		373	430	430		430	430
	Pressure	bar	1		1	1	1		1	1
	Enthalpy	kJ/kmol	-5227.852		-4001.404	-4082.670	-4082.670		-3248.183	-9451.452
	Required energy	MJ				-0.535				2.586E-08
	Compounds									
1	isobutylbenzene	kg/hr	0.0271	0	0	0.027140512	0.027141	0.001	2.71E-05	0.027113371
2	Acetic anhydride	kg/hr	0.0000	0	0	0	0	0	0	0
3	Hydrofluoric acid	kg/hr	0.0000	0	0	0	0	0	0	0
4	Acetic acid	kg/hr	0.0000	0	0	0	0	0	0	0
5	Acetyl fluoride	kg/hr	0.0000	0	0	0	0	0	0	0
6	4-isobutyl acetophenone	kg/hr	0.0000	0	0	0	0	0	0	0
7	Hydrogen	kg/batch	0.0000	0	0	0	0	0	0	0
8	iso-butyl phenyl ethanol	kg/batch	2.4368	0	0	2.436831481	2.436831	0	0	2.436831481
9	4-isobutylethylbenzene	kg/batch	19.0400	0.999	19.02096	0.01904	0.01904	1	0.01904	0
10	water	kg/batch	0.0750	0	0	0.074967897	0.074968	0	0	0.074967897
11	CO	kg/batch	0.0000	0	0	0	0	0	0	0
12	2-ethoxyethylacetate	kg/batch	392.0400	0.1	39.204	352.836	352.836	0.999	352.4832	0.352836
13	Ibuprofen	kg/batch	97.3891	0	0	97.38906332	97.38906	0	0	97.38906332
14	3-(4-isobutylphenyl)propanoic acid	kg/batch	2.4894	0	0	2.489433901	2.489434	0	0	2.489433901
15	1-(4-isobutylphenyl)ethyl chloride	kg/batch	9.6986	0	0	9.698589296	9.698589	0	0	9.698589296
16	HCL	kg/batch	0.0000	0	0	0	0	0	0	0
17	4-isobutylstyrene	kg/batch	3.8794	0	0	3.879435718	3.879436	0	0	3.879435718
	Mass	kg	527.0755		58.2250	468.8505	468.8505		352.5022	116.3483
	Total mass	kg			527.0755				468.8505	

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B. Calculations related to case study 2

B-I Example A. 6-hydroxybuspiron

B-I-1. Detailed calculation of solubility limits

The solubility limits are calculated from solute solubility data as a function of temperature and solvent-swap solvent mixture composition (for example, see Figure 5.15 in the main text). This limit is important to avoid precipitation of the solute during the solvent swap operation. The calculation procedure is given below:

Step 1. Select Temperature.

The solubility of a solute in a solvent is function of the temperature, with solubility usually increasing with temperature. However, the effect of solvent mixture composition on the solubility of the solute at a fixed temperature needs to be established for each solvent pair so that the solubility limit (saturation point) need to be identified.

Example: Let us assume that we have a mixture of solute S with an original solvent S2 and a swap solvent S1. Batch distillation is going to be used as the solvent swap operation. Select a temperature that is lower than the operating temperature, for example, 300K.

Step 2. Collect or generate solid saturation data to determine a saturation correlation

Collect data (or generate data through model-based SLE calculation tool) for solute solubility at a fixed temperature and at different solvent mixture compositions. Use the obtained data to find a correlation matching the data (see Figure 7.5). Now we have the equation that calculates the solubility of the solute as a function of the solvent mixture at a selected temperature that is lower than the operating temperature of the distillation operation.

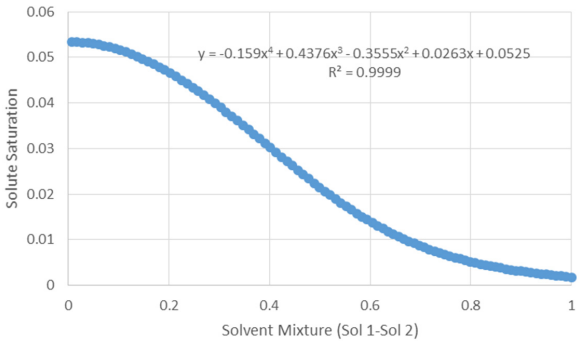

Figure 7.6 Solute solubility with respect the solvent mixture composition

Step 3. Simulation

erform simulations of the batch distillation operation for solvent swap. Use the concentration profiles obtained from simulation runs to retrieve the transient solute concentration responses. Also, use the correlation obtained in Step 2 to calculate the solid saturation composition. If the solute concentration in the batch distillation is higher than the estimated solute saturation

composition then precipitation of the solid is likely to occur. Different solubility limits can be selected using this procedure.

B-I.2 Recovery calculation

The following equation is used for the calculation of the product recovery during crystallization

$$\text{Recovery} = \frac{Initial\,amount\,(kg) - amount\ \ in\ \ mother\,liquid\,(kg)}{Initial\,amount\,(kg)} x100\% \tag{44}$$

Calculation Example 1

Consider Figure 5.18 in the main text.

Step 1. Calculate the initial amount of solute and solvents in kg

Table 5.30 gives the composition and the amount of the component after the end of the swap operation. The amount of the product is 0.0204 kmol which corresponds to 8.2 kg (MW_{solute}=401.5 kg/kmol) and the total amount of solvents is 1.39 kmol (92 kg).

Step 2. Calculate the amount of solute in the mother liquor

When cooling at 285K, the composition of solute in the mother liquor is 0.010 mol% (see Figure 5.18). Considering that the amount of the solvents has not changed, the amount of solute in the mother liquor is calculated to be 5.65 kg.

Step 3. Calculate the maximum potential recovery

Using the equation (44), the recovery is calculated

$$\text{Recovery} = \frac{8.2 - 5.65(kg)}{8.2(kg)} x100\% = \frac{2.55}{8.2} x100\% = 31\%$$

B-I.3 Regression of NRTL-SAC parameters

The parameter regression was performed through ICAS-Solvent Pro. The experimental data used for the parameter regression is given in Table 7.11 and retrieved from Watson et al. [190].

Table 7.17 Experimental solubility data in 13 solvents [190].

Solvent	Solubility (mg/ml) 6-hydroxybuspirone	Solubility (mg/ml) Buspirone	Solubility (mg/ml) Diol
DCM	446	678	0.4
Anisole	93	280	0.1
THF	301	277	3.4
DCE	260	242	0.2
Toluene	32	189	0.0
EthOAc	34	116	11
Acetone	22	88	0.2
MIBK	16	65	0.1
nBuOH	23	59	0.3
EtOH	27	54	0.2
MeCN	14	49	0.1

MTBE	14	24	0.1
IPA	11	21	0.2

Then the identified parameters are used to predict the solubility of 6-hydroxybuspirone in the remaining solvents. The predictions are shown in Figure 5.14 where the empty circles represent the solid solubility data in the eight pure solvents that were used for the regression step and the solid circles represent the predicted solid solubility values in the remaining pure solvents. The results are used to predict the solid saturation curves in different solvents as a function of temperature as shown in Figure 5.15.

B-I.4 Simulation results for ethanol and butanol

Swap solvent: Ethanol (EtOH)

Calculation of the solute saturation profile in different mixture composition at different temperatures.

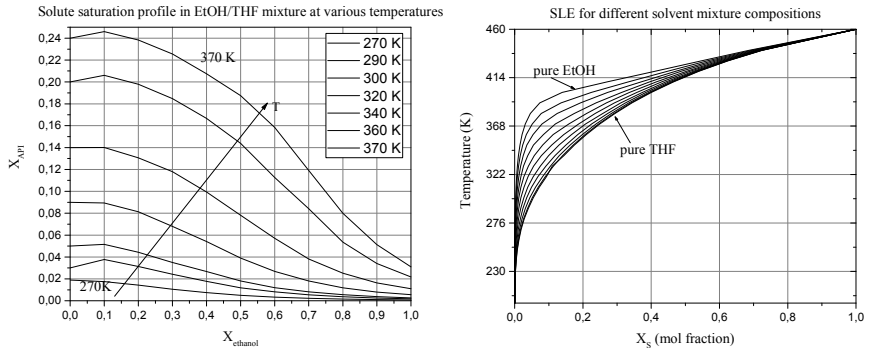

Figure 7.7 Saturation solubility of the solute as a function of the solvent mixture composition (EtOH-THF) for different temperatures (l figure on the left). Saturation solubility of the solute as a function of the temperature for different solvent mixture (EtOH-THF) composition (figure on the right).

The initial and final composition of the different charges during the operation is given in Table 7.12. The amount of the original solvents and the solute is given in Table 7.12. Swap solvent (Ethanol) is added in amount of 69kg per charge.

Table 7.18 Composition table for the batch distillation operation considering Ethanol as the swap solvent.

Compounds	**Composition 1st charge (mol %)**		**Composition 2nd charge (mol %)**		**Composition 3rd charge (mol %)**	
	Start	*End*	*Start*	*End*	*Start*	*End*
MTBE	0.049	0.02	0.010	0.000	0.000	0.00
THF	0.571	0.471	0.218	0.109	0.069	0.030
EtOH	0.374	0.490	0.764	0.879	0.922	0.957
Solute	5.00×10^{-3}	0.019	7.00×10^{-3}	0.013	0.009	0.14
Total amount in kmoles	4.04	1.05	2.79	1.56	2.31	1.50

In Figure 7.7, the volumetric composition of the still during the total operation is presented as well as the corresponding saturation curves for the recovery calculation after the end of the operation.

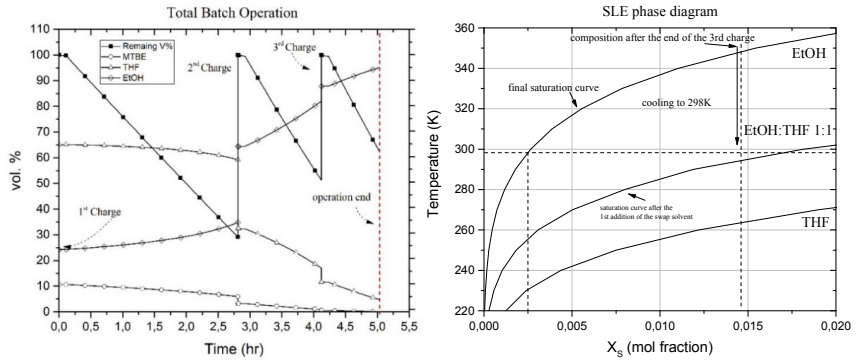

Figure 7.8 (a) Volumetric composition in the batch still during the second run and (b) calculation of the maximum potential recovery based on the corresponding SLE curve.

Swap solvent: BuOH (BuOH)

In Figure 7.8 the calculation of the solute saturation profile in different mixture composition at different temperatures is shown.

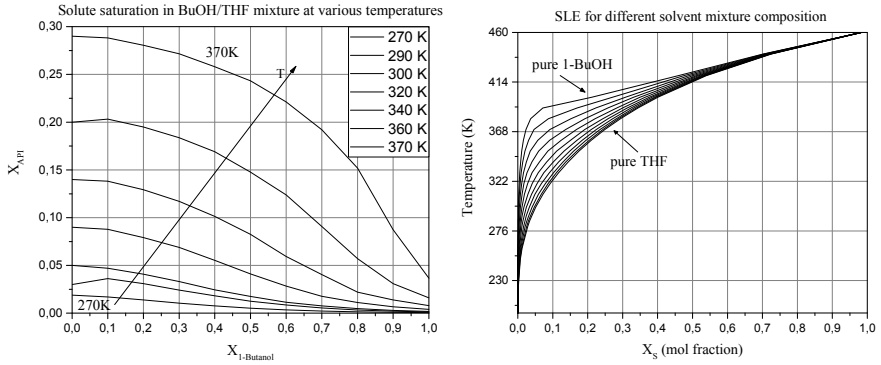

Figure 7.9 Saturation solubility of the solute as a function of the solvent mixture composition (n=BuOH-THF) for different temperatures (figure on the left). Saturation solubility of the solute as a function of the temperature for different solvent mixture (n-BuOH-THF) composition (figure on the right).

The initial (start) and final (end) composition of the different charges during the operation are given in Table 7.13. The amount of the original solvents and the solute is given in Table 7.13. Swap solvent (Butanol) is added in amount of 74kg per charge.

Table 7.19 Composition table for the batch operation considering BuOH as swap solvent.

Compounds	**Composition 1st charge (mol %)**		**Composition 2nd charge (mol %)**	
	Start	*End*	*Start*	*End*
MTBE	0.053	0.002	0.001	0.000
THF	0.655	0.131	0.058	0.003
n-BuOH	0.286	0.840	0.929	0.976
Solute	6.00×10^{-3}	0.026	0.011	0.021
Total amount in kmoles	3.476	0.786	1.786	0.976

In Figure 7.9, the volumetric composition of the still during the total operation is presented as well as the corresponding saturation curves for the recovery calculation after the end of the operation.

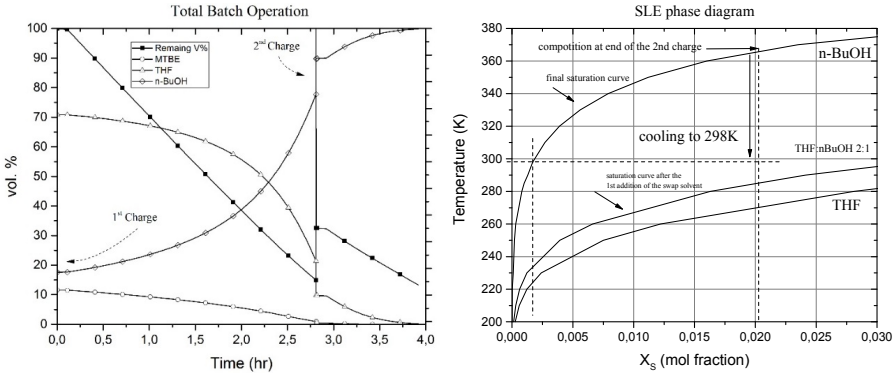

Figure 7.10 (a) Volumetric composition in the batch still during the second run and (b) calculation of the maximum potential recovery based on the corresponding SLE curve.

In, the volumetric composition of the still during the total operation is presented as well as the corresponding saturation curves for the recovery calculation after the end of the operation.

B-II Example B. Heck reaction

Table 7.20 Feasible swap solvent candidates that can replace DCM

Original solvent	Swap solvent candidate	Solvent Swap Process Classification	Vacuum effect
	Acetic Acid	Very Easy	No effect
	Acetone	Very Difficult	No effect
	THF	Easy	Negative
	iso-Hexane	Very difficult	No effect
	Methanol	Easy	No effect
	2-propanol	Very easy	Positive
	Toluene	Very easy	No effect
	Isopropyl Acetate	Very easy	Positive
DCM	Anisole	Very Easy	Weakly positive
	Methyl isobutyl ketone	Very Easy	Weakly positive
	Ethyl Acetate	Very easy	Weakly positive
	2-Methyltetrahydrofuran	Easy	Negative
	Acetonitrile	Very easy	No effect
	Water	Very easy	No effect
	N,N-Dimethylformamide	Very easy	Weakly positive
	MTBE	Very Difficult	Weakly positive
	N-Methyl pyrrolidone	Very easy	No effect

B-III Example C. Synthesis and separation

Table 7.21. The generated feasible original solvents that toluene can swap.

Original Solvent Candidate	Swap solvent	Solvent Swap Process Classification	Vacuum effect
DCM	Toluene	Very Easy	No effect
MTBE		Very Easy	No effect
Acetone		Very Easy	Positive
iso-Hexane		Very Easy	Positive
Methanol		Conditional	Negative
THF		Very Easy	No effect
EtOAc		Easy	Weakly positive
MeTHF		Very Easy	Weakly positive
MEK		Easy	Weakly positive
MeCN		Conditional	No effect
IPA		Conditional	Positive
IPAc		Very Difficult	Weakly positive
water		Conditional	Weakly negative

B-IV Example D. Ketone intermediate for the LY500307 synthesis

Table 7.22. The generated swap solvents which can replace ethyl acetate.

Original Solvent Candidate	Swap solvent	Solvent Swap Process Classification	Vacuum effect
EtOAc	Acetic Acid	Easy	Weakly Positive
	2-propanol	Conditional	Positive
	Toluene	Easy	Weakly Positive
	Anisole	Very easy	Weakly Positive
	MIBK	Easy	Weakly Negative
	NMP	Easy	No effect
	Water	Conditional	No effect
	DMF	Very easy	Weakly Positive
	Ethanol	Difficult	Positive
	1-butanol	Very easy	Weakly Positive
	2-methyl-1-propanol	Very easy	No effect

C. Calculations related to case study 3

C-I Model development for reaction-separation equipment.

Phase I: Functional Description

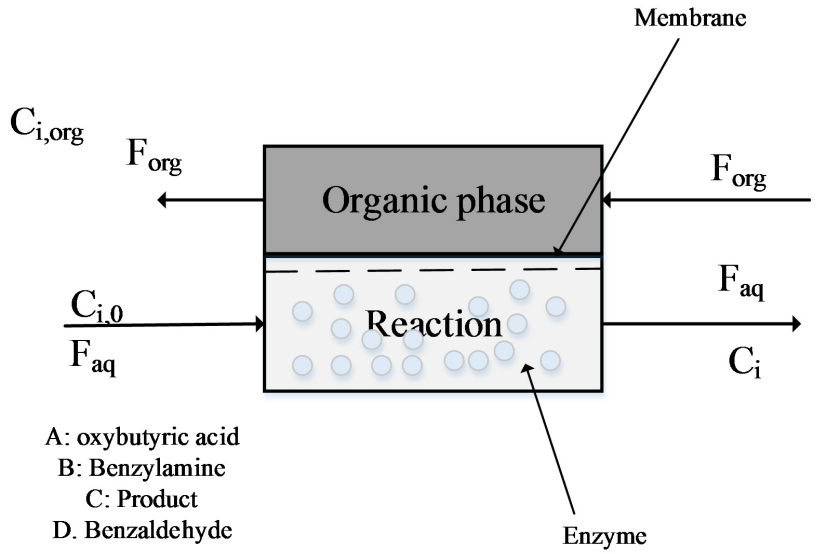

Figure 7.11. System description for EMR, reaction-separration systems

Phenomena:

1. Equilibrium controlled reaction (by product enzyme inhibition)
2. Mass transfer aqueous-organic phase
3. Membrane separation

Phase II: Model construction

Table 7.23. Mass balance equation for EMR, reaction-separration systems

Description	Equation	Number of equations
Balance Equations		
Reaction in aqueous phase	$\frac{dc_i}{dt} = \frac{(c_{i,0} - c_i)F_{aq}}{V_{aq}} + v_i r - J_i \; ; where \; i = A,B,C,D$	4
Initial conditions	$t = 0 \rightarrow c_i = c_{i,0} \; ; where \; i = A,B,C,D$	
Extraction	$\frac{dc_{i,org}}{dt} = \frac{(c_{i,org,0} - c_{i,org})F_{org}}{V_{org}} + J_i \frac{V_{aq}}{V_{org}} ; \; where \; i = A,B,C,D$	4
Initial conditions	$t = 0 \rightarrow c_{i,org} = c_{i,org,0} \; ; where \; i = A,B,C,D$	

Table 7.24 Constitutive equations for EMR, reaction-separration systems

Description	Equation	Number of equations
Constitutive equations		
Reaction Rate	$r = k \cdot \left(c_A \cdot c_B - \frac{c_C \cdot c_D}{K_{eq}} \right)$	1
Viscosity	$\mu_i = 6x10^{4} \cdot \exp\left(A_{\mu i} + B_{\mu i}/T + C_{\mu i} \ln T + D_{\mu i} T^{E_{\mu i}} \right)$	4
Density	$\rho_i = MW_i \left[\left(A_{\rho i} / B_{\rho i} \right)^{\left(1+\left(1-T/C_{\rho i}\right)^{D_{\rho i}}\right)} \right]$	4
Log mean diameter	$d_{lm} = \frac{d_{in} - d_{out}}{\ln\left(d_{in}/d_{out}\right)}$	1
Mass transfer coefficient in the fiber	$k_{w,i} = 1.62 \mathrm{Re}^{\frac{1}{3}} \left(\frac{\mu_i}{\rho_i L} \right)^{\frac{1}{3}} \left(\frac{D_i}{d_{in}} \right)^{\frac{2}{3}}$	4
Overall mass transfer coefficient	$\frac{1}{K_{aq-org,i}} = \left(\frac{1}{k_{w,i}} + \frac{p_i d_{in}}{d_{lm} k_m} + \frac{p_i d_{in}}{d_{out} k_o} \right)$	4
Alpha	$\alpha_i = 2 \cdot \pi \cdot r \cdot N \cdot K_{aq-org} \cdot \left(\frac{1}{F_{in}} - \frac{p_i}{F_{org}} \right)$; *where* $i = A,\mathrm{B},\mathrm{C},\mathrm{D}$	4
Equilibrium concentration in the org. phase	$c_i^* = \frac{1}{p_i} \frac{F_{aq}\left(1 - \exp\left(\alpha_i L\right)\right)}{F_{aq} - F_{org}/p_i} \mathrm{c_i}$; *where* $i = A,\mathrm{B},\mathrm{C},\mathrm{D}$	4
Mass transfer	$J_i = k_{aq-org} \left(c_i - \frac{c_i^*}{p_i} \right)$	4

Table 7.25 Model analysis for EMR, reaction-separration systems

Type of equation	Number of equations
ODEs	8
Algebraic	30
Total number of variables	112
Degree of Freedom	74

Table 7.26 Variables classification for EMR, reaction-separration systems

	Variables Types	Symbol	Number of Variables	Total Number
To be specified	System Variables	$c_{i,0}$, F_{aq}, V_{aq}, v_i, $c_{i,0,org}$, F_{org}, V_{org}, d_{in}, d_{out}, Re, L, D_i, p_i, k_o, r, N, Mw_i, $A_{\rho i}$, $B_{\rho i}$, $C_{\rho i}$, $D_{\rho i}$, $A_{\mu i}$, $B_{\mu i}$, $C_{\mu i}$, $D_{\mu i}$, $E_{\mu i}$, T	71	
	System Parameters	k, K_{eq},	2	
	Known Variables	π	1	74

To be predicted	Algebraic (explicit)	R, J_i, d_{lm}, $k_{w,i}$, $K_{aq\text{-}org,i}$, α_i, c_i^*, ρ_i, μ_i	30	
	Dependent Variables	c_i, $c_{i,org}$	8	38

Table 7.27 Variables values for EMR, reaction-separration systems

	Specified Value	***Units***
Dependent variables		
c_i	[0,0,0,0]	mol/lt
$c_{i,org}$	[0,0,0,0]	mol/lt
System Variables		
F_{aq}	0.9	lt/hr
V_{aq}	1	Lt
$c_{i,0}$	[0.1,0.14,0,0]	mol/lt
$c_{i,org,0}$	[0,0,0,0]	mol/lt
v_i	[-1, -1, 1, 1]	-
V_{org}	5	Lt
F_{org}	4.5	Lt/hr
d_{in}	0.2	cm
d_{out}	0.6	cm
L	1	cm
D_i	[$2x10^{-8}$, $2x10^{-8}$, $2x10^{-8}$, $2x10^{-8}$]	cm^2/hr
p_i	[1.014, $1.20x10^5$, $1.24x10^{-4}$, $2.22x10^5$]	-
k_o	0.0138	cm/hr
k_m	0.324	cm/hr
r	0.024	cm
N	3600	-
Re	0.02	-
MWi	[102.09, 107.15, 106.12, 103.12]	gr/mol
T	310	K
[$A_{\rho i}$, $B_{\rho i}$, $C_{\rho i}$, $D_{\rho i}$]	Table 7.29	-
[$A_{\mu i}$, $B_{\mu i}$, $C_{\mu i}$, $D_{\mu i}$, $E_{\mu i}$]	Table 7.29	-
System parameters		
k	191	lt/(mol hr)
Keq	0.434	-
Known variables		
π	3.14	-

Table 7.28. Coefficient for density calculation from ICAS

	$A_{\rho i}$	$B_{\rho i}$	$C_{\rho i}$	$D_{\rho i}$
A	4.49602	0.56245	550	2
B	0.7111	0.26525	683.5	0.13446
C	1.11898	0.25625	688	0.4249
D	0.79368	0.25711	695	0.2863

Table 7.29 Coefficient for viscosity calculation from ICAS

	$A_{\mu i}$	$B_{\mu i}$	$C_{\mu i}$	$D_{\mu i}$	$E_{\mu i}$
A	-11.42	1702.18	-0.00011184	$1.04x10^{-10}$	2
B	-12.192	1567.7	0.0883	0	0
C	-17.062	1609.3	0.0891	0	0
D	-11.42	1702.18	-0.00011184	$1.04x10^{-10}$	2

Section C. Separation Process synthesis

Table 7.30 Pure compound properties for the compound involved in ω-transamination, where A: water, B: benzylamine, C: 2-oxybutyric acid, D: L-2-aminobutyric acid, BD: benzaldehyde, and F: hexane

		MW (gr/mol)	BP (K)	MP (K)	SP ($MPa^{½}$)	Mv ($kmol/m^3$)	VP	RG(Å)
A	**water**	18	373.15	273.15	47.81	0.018		0.615
B	**BA**	107	458.15	227	21.7	0.109		3.837
C	**OA**	102.09	476.45	306.15	23.29	0.09	64.26	0
D	**AABA**	103.12	477.42	573.15	22.18	0.11		0
E	**BD**	106.12	452.15	247.15	21.6	0.102		3.751
F	**Hexane**	86.18	341.85	177.85	14.9	0.131		3.769

D. Calculation related to case study 4

Table 7.31 Kinetic parameters for glucose isomerization as a function of the temperature adapted by [205].

T (K)	v_{mf} (mmol/min/lt)	v_{mr} (mmol/min/lt)	k_{mf} (mol/m^3)	k_{mr} (mol/m^3)	K_{eq}	X_{eq}
333.15	4.75	3.11	700	450	0.98	0.49
338.15	6.84	5.13	760	590	1.03	0.51
343.15	9.14	7.93	850	840	1.14	0.53
348.15	12.46	12.35	920	1110	1.22	0.55
353.15	15.98	17.92	1020	1580	1.39	0.58

Table 7.32 The Arrhenius parameters for glucose isomerization as they have been calculated from the data given in Table 7.32.

j	v_{mf}	v_{mr}	k_{mf}	k_{mr}
A_j	1.37×10^6	1.29×10^{17}	5.46×10^5	1.90×10^{12}
E_j	5.92×10^4	8.58×10^4	1.85×10^4	6.15×10^4

Table 7.33 Systems Variables for the glucose isomerization reactor model

System Variables	*Value*	*Source*
w	560-3000kgr$_{cat}$	Novo
θ	55-60^{o}C	Novo
wt%	45-52	Novo
F_0	3.6-6 m^3 hr^{-1}	Novo
d_b	0.5-1.8 m	Novo
H	2.5-4.3m	Novo
ε	0.36	[211]
D_m	1.38×10^{-4} m^2 d^{-1}	[211]
d_p	0.0002-0.0004 m	[211]
μ	0.12 kg m min^{-1}	Correlation
ρ	1100 kg m^{-3}	[211]
ρ_{cat}	1*	[205]
R_p	0.0001-0.0002	[211]
DS	45	Novo
DP	100	Novo
Xi (%)	0-5	Novo
pHout	7.4-7.6	Novo
pHin	7.5	Novo
R	8.314 J mol^{-1} K^{-1}	-

*included in reaction kinetics

Table 7.34 Process conditions for glucose isomerization

Process Operation Variables	***Value***	***Source***
Weight of Catalyst, W	560 kgr_{cat}	Novo
Temperature, T	55-70 ^oC	Novo
Inlet concentration $[S]_0$	45-50% w/w	Novo
Initial Flowrate, F_0	3.6 -17.5 $m^3\ hr^{-1}$	Novo
Bed Diameter, d_b	0.8 m	Novo
Bed length, H	3.3 m	Novo

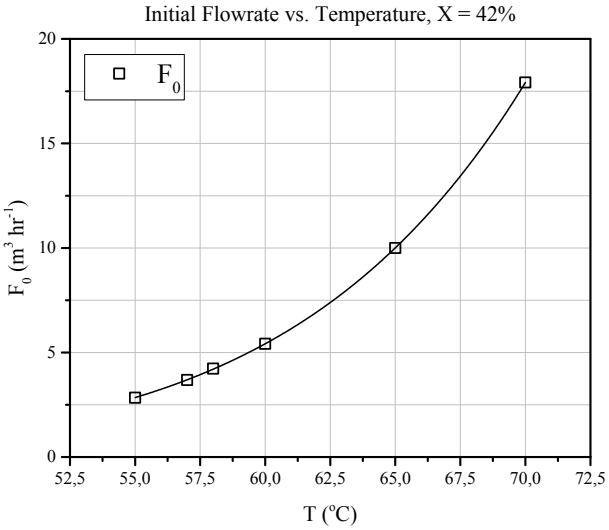

Figure 7.12 Initial flowrate vs. temperature for the process variables for glucose isomerization given in Table 7.34.

Table 7.35 Process conditions for glucose isomerization

Process Operation Variables	***Value***	***Source***
Weight of Catalyst, W	3000 kgr_{cat}	Novo
Temperature, T	55 ^oC	Novo
Inlet concentration $[S]_0$	50% w/w	Novo
Initial Flowrate, F_0	15.5 $m^3\ hr^{-1}$	Novo
Bed Diameter, d_b	1.6 m	Novo
Bed length, H	5 m	Novo

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